DIPLOMARBEIT

Titel der Diplomarbeit

Synthesis of 2,2’,3,3’-tetrasubstituted binaphthyl derivatives and novel approaches to enantiopure 2,2’-dibromo-1,1’-binaphthyl

angestrebter akademischer Grad

Magister der Naturwissenschaften (Mag. rer. nat.)

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Studienrichtung (lt. Studienblatt):	A419 Chemie
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Wien, am 6. Oktober 2008

Zu Beginn möchte ich mich bei meinen Eltern bedanken. Für den familiären Rückhalt, ihr Vertrauen und ihre Unterstützung bei meinem Weg durch das Studium.
Mein Dank gilt auch Mag. Adolf Weilguny, der mich in der Schule für Chemie begeisterte. Sein Engagement war letztlich entscheidend, dass ich diese Studienrichtung eingeschlagen habe.
Für die interessante Themenstellung und die exzellente Betreuung während der Diplomarbeit möchte ich mich bei Prof. Dr. Michael Widhalm bedanken. Aus den unzähligen interessanten Gesprächen und Diskussionen mit ihm habe ich viel gelernt. Gesondert erwähnen möchte ich in diesem Zusammenhang auch die freundliche und entspannte Arbeitsatmosphäre in der Gruppe.
Für die angenehme Zeit im Labor möchte ich weiters meinen Kollegen danken, speziell Richard Turetschek, Michael Vogl und Michael Abraham. Darüber hinaus natürlich meinen sonstigen Freunden und Bekannten, mit denen ich auch außerhalb der Universitätsmauern viele schöne Stunden verbracht habe.
Besonderen Dank möchte ich auch Doz. Dr. Lothar Brecker aussprechen, der bei jeglichen Fragen und Problemen in Bezug auf NMR Spektroskopie immer erster Ansprechpartner war.
Für die Durchführung einer Kristallstrukturanalyse möchte ich Prof. Dr. Vladimir Arion und Alexander Roller danken.

I Contents

II Abbreviations

Ar	aryl
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
BINOL	1,1’-binaphthyl-2,2’-diol
Bn	benzyl
Bu	butyl
Bz	benzoyl
COD	1,5-cyclooctadiene
DMSO	dimethylsulfoxide
CPME	cyclopentyl methyl ether
CSA	camphorsulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DABN	2,2’-diamino-1,1’-binaphthyl
DBBN	2,2’-dibromo-1,1’-binaphthyl
DIBN	2,2’-diiodo-1,1’-binaphthyl
DIPAMP	1,2-bis[(2-methoxyphenyl)phenylphosphino]ethane
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
EI	electron ionization
ESI	electrospray ionization
etc	*et cetera*
GC	gas chromatography
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
HYTRA	2-hydroxy-1,2,2-triphenylethyl acetate
Ipc	isopinocampheyl
iPr	isopropyl
LDA	lithium diisopropylamide
MOM	methoxymethyl
MS	mass spectrometry

NBS	N-bromosuccinimide
NMR	nuclear magnetic resonance
PE	petroleum ether
RT	room temperature
THF	tetrahydrofuran
Tf	trifluoromethylsulfonyl (triflyl)
TMEDA	N,N,N',N'-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl

1 Introduction

1.1 Chirality and the relevance of chiral substances

Objects that can't be superimposed onto their mirror image are chiral. In a chemical context, a structure and its not superimposable mirror image are said to be enantiomeric, and pairs of species with said relationship are called enantiomers.

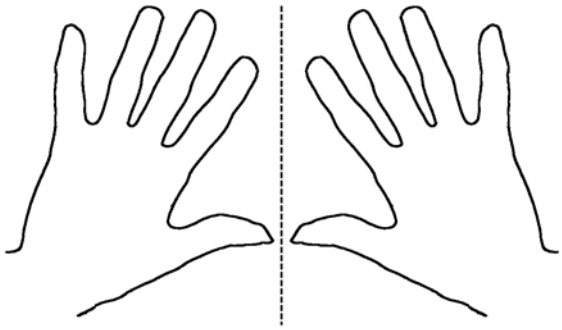


Figure 1. Our hands are examples of chiral objects. Left and right hand are mirror images of each other, they are enantiomers.

Many of the molecules making up life on earth are chiral: of the 20 standard proteinogenic amino acids all but one, glycine, are chiral.[1] Thus proteins, being composed of amino acids, are also chiral. Most monosaccharides are chiral, consequently oligo- and polysaccharides, carbohydrates and nucleic acids, all

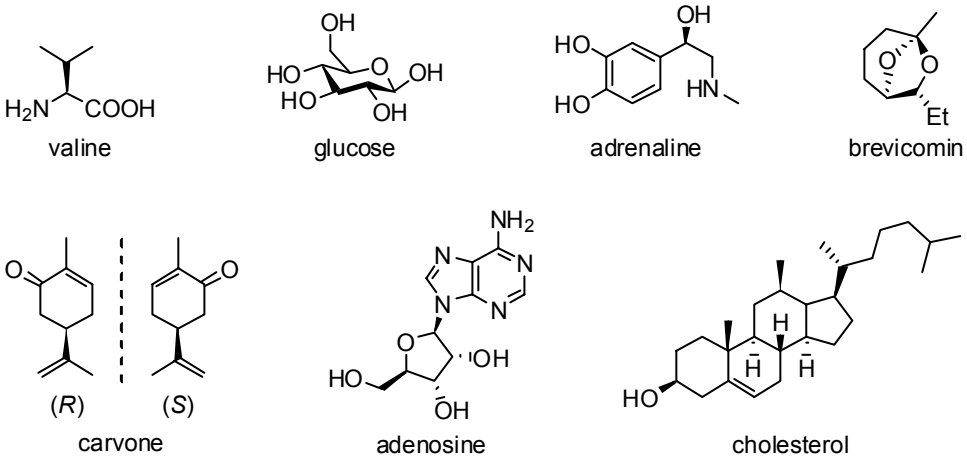


Figure 2. Examples for naturally occurring chiral molecules: valine, an amino acid; glucose, a monosaccharide; adrenaline, a neurotransmitter; brevicomin: an insect pheromone; carvone: a monoterpene; adenosine: a neurotransmitter; cholesterol: a hormone.

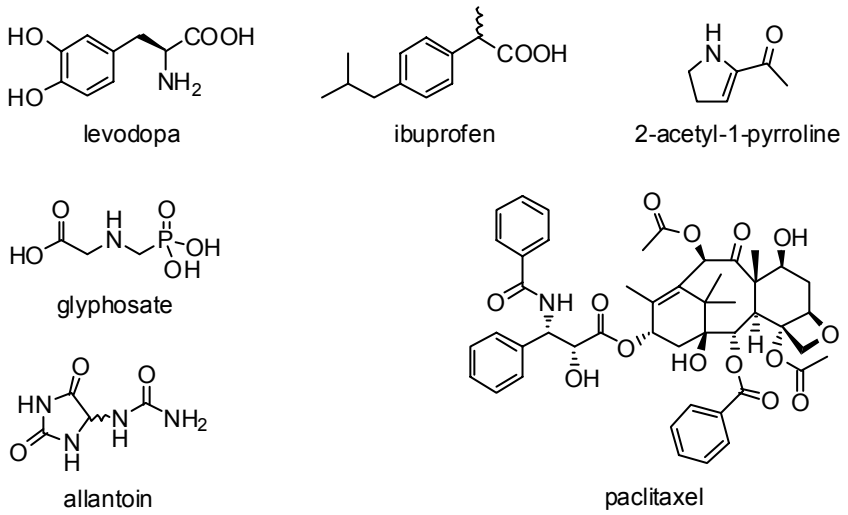


Figure 3. Natural and synthetic drugs, fragrances, pesticides and cosmetics: Levodopa, a drug sold as single enantiomer; ibuprofen: a racemic drug; 2-acetyl-1-pyrroline, an aroma compound smelling like cooked rice;[4,5] glyphosate, an achiral broad spectrum herbicide, marketed under the trade name Roundup®;[6,7] allantoin, a compound used in cosmetics;[8] paclitaxel, a natural product used in cancer therapy.[9]

containing saccharide units, are chiral too.

Many other small molecules synthesized by living beings are also chiral (Figure 2). Some neurotransmitters and many hormones, pheromones and aroma compounds are chiral. An interesting example is the monoterpene carvone found in plants: (*S*)-carvone smells like caraway while (*R*)-carvone smells like spearmint.[2] The (*R*) and (*S*) enantiomers of limonene also have a different smell, reminiscent of oranges and lemons, respectively.[3] These findings are strong indications that the olfactory receptors in our nose are chiral, responding differently to enantiomeric forms of scents.

Synthetic and natural drugs have long been used to influence living systems.[10] Examples include pharmaceutical products, cosmetics, fragrances, pesticides, *etc* (Figure 3). As the molecules making up life are chiral, organisms react differently to the two enantiomeric forms of a molecule.

With this in mind, three principal kinds of compounds can be distinguished:

- racemic mixtures
- achiral compounds
- enantiopure compounds

Racemic mixtures are easy to synthesize, but obviously contain the undesired enantiomer, too. The “wrong” enantiomer may have similar effects as the desired one, it

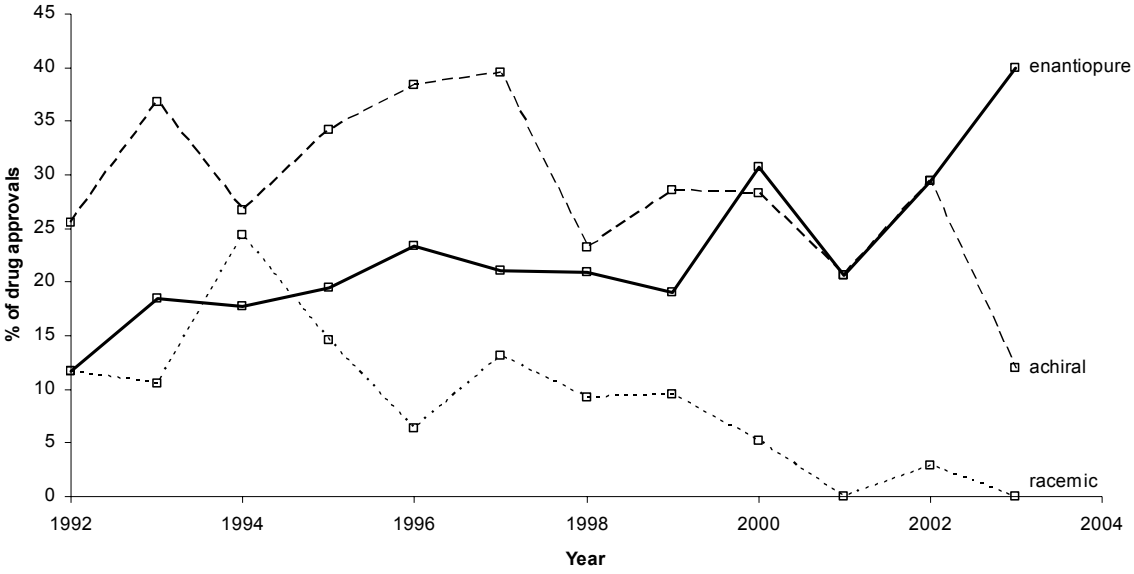


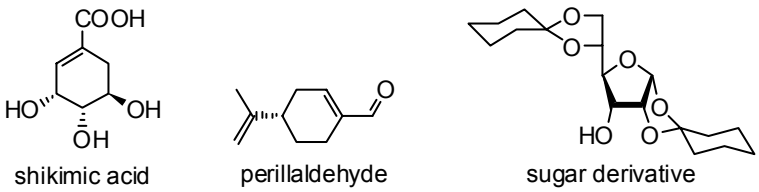
Figure 4. FDA drug approvals: the percentage of achiral and racemic drug approvals is decreasing; enantiopure drugs become more common. Graph based on literature data.[12]

may be inactive, but it can even have detrimental properties. While the latter is clearly problematic, also inactivity can cause trouble: at the very least, higher dosages are required to achieve the same outcomes which amplifies possible side effects and degradation issues. As a consequence, racemic drugs (for example) are being more and more frowned upon.[11]

With achiral compounds, the complexities of chiral synthesis are also avoided. However, the restriction to achiral molecules severely limits the available chemical space, foregoing potentially more potent chiral substances.

Single enantiomers are typically more difficult or expensive to produce: enantiopure starting materials frequently cost more than the corresponding racemic mixtures, since enantioselective synthesis requires special catalysts, auxiliaries or the like. During further steps of the synthesis racemization of intermediates can also be a problem.

Nonetheless, asymmetric synthesis is becoming more practical and economically feasible all the time, furthermore it avoids the disadvantages of racemic and achiral compounds. Therefore, enantiopure substances find more widespread use. An interesting example is provided by an analysis of drug approvals by the U.S. Food and Drug Administration (FDA):[12] while the percentage of single enantiomer compound approvals is increasing, the numbers for achiral and, especially, for racemic drugs are declining (Figure 4).



shikimic acid perillaldehyde sugar derivative

Figure 5. Chiral pool starting materials: shikimic acid is used in the synthesis of oseltamivir (an influenca drug marketed as Tamiflu);[15] perillaldehyde is used in a total synthesis of platencin;[16] the sugar derived building block to the right is used in a total synthesis of crocacin.[17]

Apart from the industrial importance of enantiopure substances, synthesis of single enantiomers is also of academic interest. A huge number of papers dealing with enantioselective total syntheses of natural products are published every year.[13] Moreover, chiral compounds are also used for the elucidation of reaction mechanisms[14] and for studies on biological systems.

1.2 Synthesis of enantiopure compouonds

As there is definitely a need for enantiopure compounds, the question of synthetic access arises. Nonracemic substances can't emerge only from achiral or racemic materials; thus, enantiopure starting materials, reagents or catalysts are required to obtain single enantiomers as products. There are several different approaches which are outlined below.

1.2.1 Chiral starting materials

Nonracemic starting materials are typically obtained from the chiral pool (enantiopure natural products), for example in the form of amino acids, sugars, terpenes, *etc*.[18] They are relatively cheap and are available in very high enantiomeric purity. A serious limitation of the method is that usually only one specific enantiomer is occurring naturally. Typically, careful planning of the synthesis is necessary to incorporate the stereogenic center with the desired configuration in the product and to avoid racemization (which can occur under harsh reaction conditions and is especially likely if the stereocenter is in α-position to electron withdrawing groups) during latter steps. Some chiral pool starting materials that have been used in synthesis are shown in Figure 5.

1.2.2 Optical resolution

Resolution of chiral compounds means separating the two enantiomers of a racemic mixture.[19] A practical limitation of this approach is that the maximum yield of the desired enantiomer is 50 %. If both enantiomers are of interest (which is often the case for chiral catalysts and their precursors), this is not problematic; otherwise it can be a significant disadvantage.

Several methods for the resolution of racemic mixtures exist:

The racemate may be reacted with an enantiopure resolving agent to give a mixture of diastereomers, which can be readily separated by a variety of techniques. Subsequent cleavage and separation of the derivatizing agent then gives the enantiopure product. While this approach is simple in theory, a stoichiometric amount of resolving agent is required for the two step procedure. High yielding conversions, quantitative separations and a high recovery rate of the resolving agent are necessary to make such a process economical. However, these points are only seldom met in reality. The most common variant is selective crystallization of one enantiomer with a chiral reagent forming salts or inclusion complexes (clathrates).[20] This allows easy recovery and recycling of unreacted resolving agent and facile liberation of the pure enantiomer. Common resolving agents for carboxylic or sulfonic acids are shown in Figure 6, for amines in Figure 7.

Kinetic resolution[21] exploits the difference in conversion rates of two enantiomers when reacting with enantiopure reagents. In favorite cases sufficient rate differences arise, making the reaction of one enantiomer complete before significant amounts of the

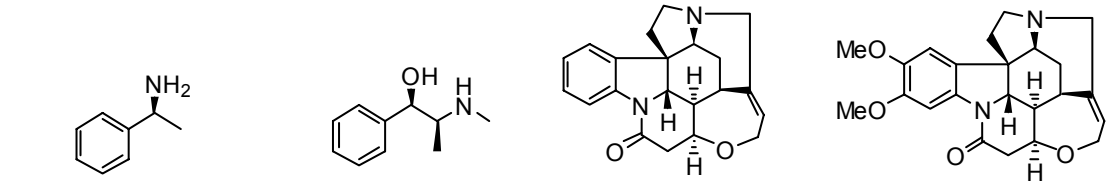


Figure 6. Chiral agents for resolving acids.

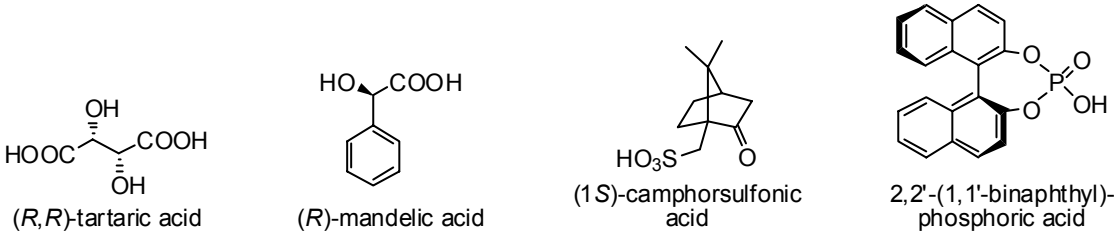
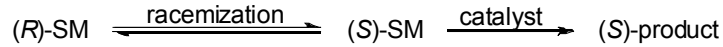


Figure 7. Chiral agents for resolving amines.



Scheme 1. Dynamic kinetic resolution: the equilibrium between the enantiomers of the starting material (SM) is pulled towards the desired enantiomer, since only that reacts to the product.

second one have reacted. A particular advantage is that the process can be made catalytic, so that small amounts of enantiopure agent suffice. In practice, mostly enzymes are used for kinetic resolutions as they discriminate very sharply between enantiomers. Other advantages are the high turn over frequencies and turn over numbers, allowing short reaction times and low catalyst loadings.

The inherent shortcoming of resolution procedures, the 50 % waste of the undesired enantiomer has been overcome with the development of dynamic kinetic resolution.[22] It combines the racemization of starting material with kinetic resolution, as depicted in Scheme 1.

Several chromatographic techniques have been used for resolution of racemic mixtures, exploiting the different stabilities of transient associates between the enantiomeric analytes and a chiral stationary phase. While both, chiral gas chromatography (GC) and high pressure liquid chromatography (HPLC), are common in analytical applications, only LC allows practical separations on preparative scale.

1.2.3 Asymmetric synthesis

"Asymmetric synthesis" means producing enantiopure compounds from achiral starting materials (without resorting to resolution). It includes methods based on auxiliaries, chiral reagents and chiral catalysts.[23]

With the auxiliary approach, an enantiopure auxiliary is first covalently linked to the starting material. Further reactions creating a stereogenic center are then carefully designed to give only one diastereomer by asymmetric induction. The final enantiopure product is obtained after cleavage of the auxiliary, which can be recovered and reused. Most of the known auxiliaries are derived from the chiral pool,[24] with the same advantages and limitations as mentioned before. A further negative aspect of auxiliary based chemistry is the need for two additional steps: auxiliary attachment *and* cleavage.

The first application of this technique probably dates back to Corey in 1975, who used phenylmenthol in his synthesis of a prostaglandin intermediate.[25] Nowadays other auxiliaries are used, offering improved asymmetric induction and being more

phenylmenthol (*S*,*S*)-pseudoephedrine an oxazolidinone a thiazolidinethione

Figure 8. Examples of auxiliaries: phenylmenthol as used by Corey; pseudoephedrine; an oxazolidinone which is commonly used in Evans' aldol reactions and a thiazolidinethione which is common for Crimmins' aldol reactions.

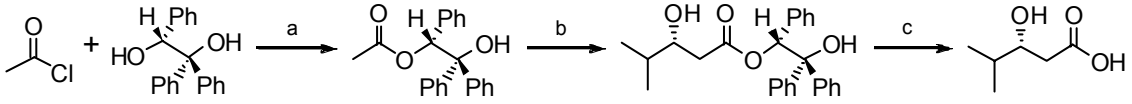


Figure 9. An example of an asymmetric synthesis using (*R*)-HYTRA. Reagents and conditions: a) pyridine, CH_2Cl_2, 0 °C to RT, 4 h; b) LDA, THF, 0 °C, then 2-methylpropanal, –126 °C, 90 min; c) KOH, water, methanol, reflux, 3 h. (HYTRA = 2-hydroxy-1,2,2-triphenylethyl acetate, LDA = lithium diisopropylamide)

conveniently prepared than the aforementioned phenylmenthol. Popular auxiliaries include Evans' oxazolidinones, the related thiazolidinones[26] and pseudoephedrine.[27] Some examples are shown in Figure 8, an exemplary reaction sequence is outlined in Figure 9.[28]

Alternatively, chiral reagents can be applied to obtain chiral products. Compared to auxiliaries, no additional reaction steps are required. However, although recycling of the expensive chiral reagent is possible in theory, it's often too troublesome to be practical. Thus this method can become rather expensive, especially on larger scale.

Widely known examples include allylations and crotylations, such as Brown's[29] and Rousch's[30] procedures, stereoselective alkyne additions to aldehydes,[31] and α-hydroxylation of ketones via Davis' oxaziridine.[32]

A third method, synthesis of chiral products through asymmetric catalysis, has become increasingly popular during the last decades. The features and opportunities of this elegant approach to enantiopure compounds deserve a more thorough discussion.

1.3 Asymmetric catalysis

In theory asymmetric catalysis allows the use of only tiny quantities of expensive chiral material to synthesize any amount of chiral product. This avoids the problems of auxiliary based approaches (the increased number of steps and the recovery of the

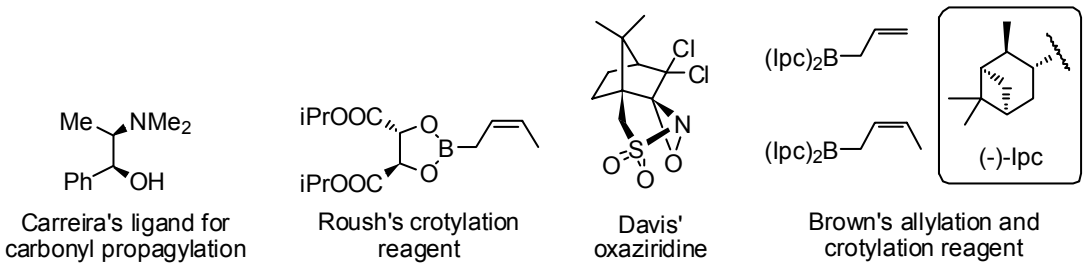


Figure 10. Reagents used in asymmetric synthesis. (Ipc = isopinocampheyl)

auxiliary after cleavage) and chiral reagents (the large consumption of enantiopure material). Today asymmetric catalytic procedures are known for a wide variety of transformations. High enantiomeric excesses (> 99 %) and high yields are routinely achieved.

Different catalytic approaches, such as organocatalysis, phase transfer catalysis, transition metal catalyzed transformations, *etc* were shown to be amenable to asymmetric variants. Today a large variety of products is available *via* asymmetric catalytic transformations.

Due to the broad range of catalyst- and reaction type, the following pages can only show some highlights.

1.3.1 Transition metal catalyzed asymmetric hydrogenations

Historically one of the first enantioselective catalytic processes was metal catalyzed hydrogenation. Perhaps the most widely known example is the synthesis of L-dopa (used to treat Parkinson's disease) *via* stereoselective reduction of an enamine precursor and subsequent hydrolysis.[33] The development of the chiral DIPAMP ligand for this application earned William Knowles the Nobel Price in 2001.[34] The same year also

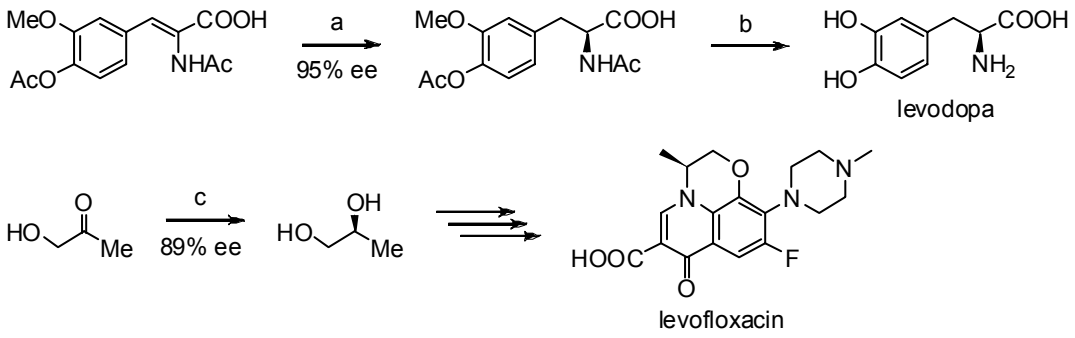


Figure 11. Asymmetric levodopa and levofloxacin syntheses. Reagents and conditions: a) $[Rh((R,R)\text{-DIPAMP})COD]^+ BF_4^-$, H_2; b) H_3O^+; c) $Ru((R)\text{-BINAP})_2Cl_2$, H_2.

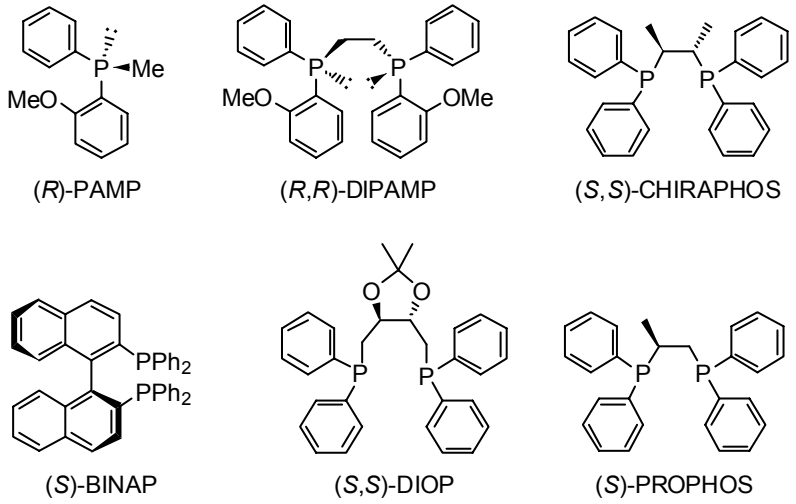


Figure 12. Common chiral phosphine based ligands.

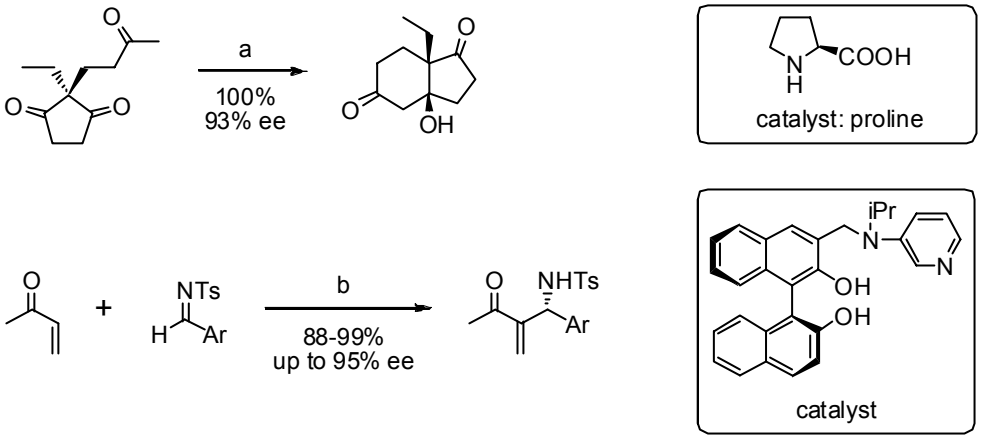


Figure 13. Organocatalytic reactions. Reagents and conditions: a) 3 mol% proline, DMF, RT, 20 h; b) 10 mol% catalyst, toluene, CPME, –15 °C. (DMF = N,N-dimethylformamide, CPME = cyclopentyl methyl ether, Ts = *p*-toluenesulfonyl)

Ryoji Noyori was honored for the development of the 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) ligand[35], which proved useful for a wide range of catalytic applications and is used in the synthesis of the antibiotic levofloxacin. Both reactions are shown in Figure 11; Figure 12 gives an overview of some common chiral phosphine ligands.

1.3.2 Organocatalysis

Since the first demonstration of organocatalysis in 1971, transformations promoted by small organic molecules as catalysts are becoming increasingly popular.[36] Starting from proline derived catalysts, mostly used for Michael or aldol reactions, many more

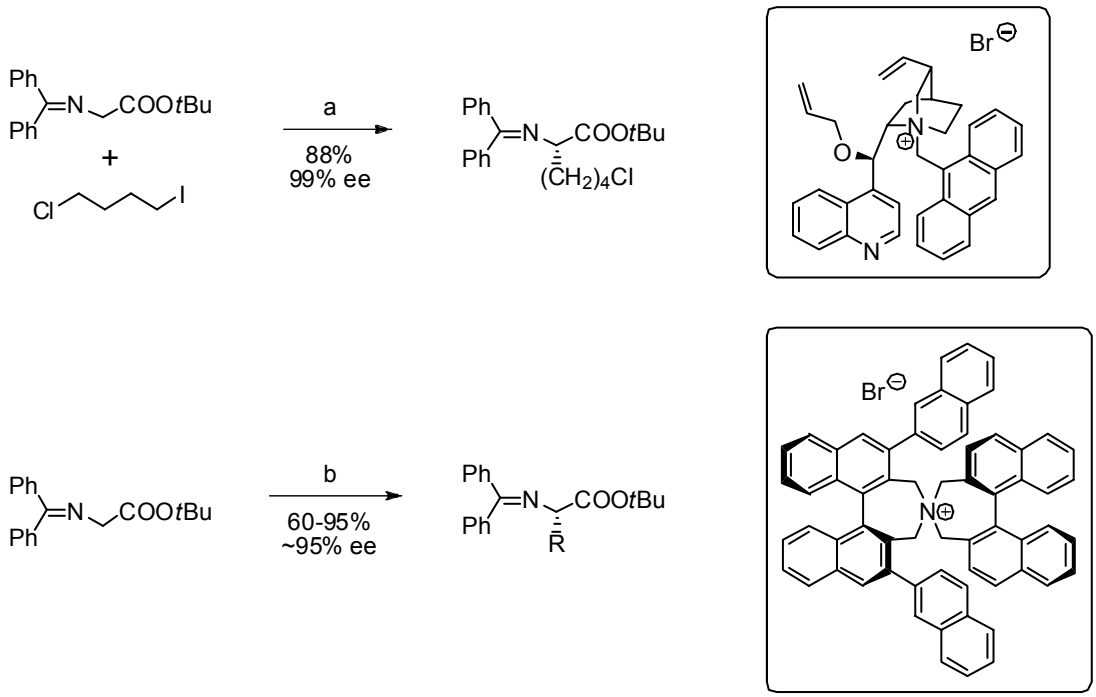


Figure 14. Phase transfer cataylsis: a) 10 mol% catalyst, $CsOH \cdot H_2O$, CH_2Cl_2, –78 °C; b) 1.2 eq R-X, 1 mol% catalyst, toluene, aqueous KOH; 0 °C.

variations of this concept are known today. They do not suffer from drawbacks that metal catalyzed reactions usually have: high cost of precious metal precursors, difficult purification of the product and sensitivity to air and/or water.[36]

Typical mechanisms are enamine, iminium and Brønsted acid catalysis. Two typical examples are shown in Figure 13: the proline catalyzed asymmetric aldol reaction reported by Hajos and Parrish[37] and an aza-Baylis-Hillman reaction catalyzed by a binaphthyl derivative.[36]

1.3.3 Phase transfer catalysis

Chiral phase transfer catalysis is also an efficient method of transferring chiral information into prochiral substrates. An interesting example is the synthesis of chiral amino acids under phase transfer conditions, with *cinchona* alkaloid derivatives[38] or binaphthyl derivatives[39] as catalysts (Figure 14). These reactions allow facile access to important natural and unnatural amino acids with excellent yield and enantioselectivity.

1.3.4 Asymmetric Lewis acid catalysis

Lewis acids can promote Diels-Alder and other electrocyclic reactions, Michael additions, Friedel-Crafts reactions, Strecker reactions and many more.[40] It is assumed

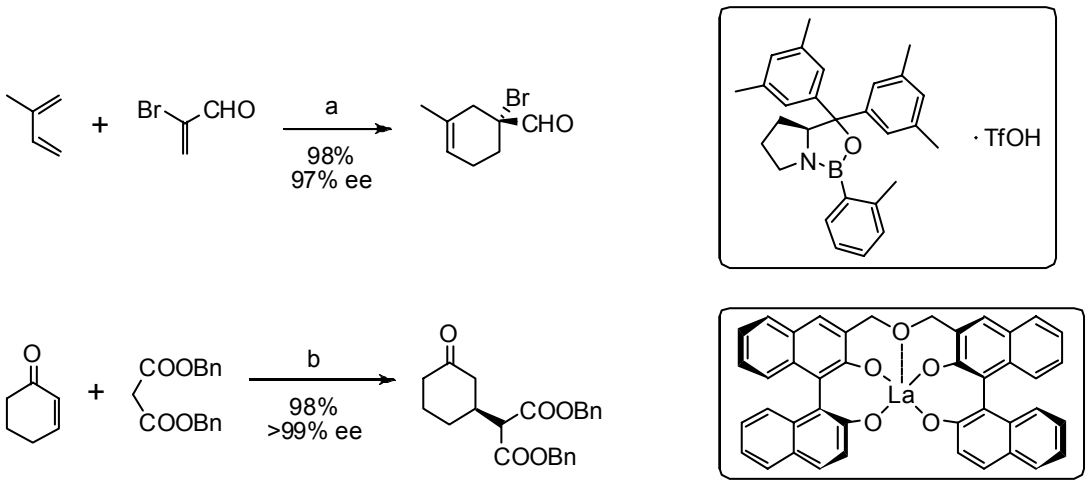


Figure 15. Asymmetric Lewis acid catalyzed reactions. Reagents and conditions: a) 6 mol% catalyst, CH_2Cl_2, –95 °C, 1 h; b) 10 mol% catalyst, DME, 4 °C, 85 h. (Tf = trifluoromethylsulfonyl, Bn = benzyl, DME = dimethoxyethane)

that Lewis acid attack on the carbonyl oxygen increases the electrophilicity of the carbonyl C atom and the adjacent π-system. Several chiral Lewis acid catalysts have been developed; Figure 15 shows some examples.

1.4 Binaphthyl – a versatile chiral scaffold

In the previous section about asymmetric catalysis several 1,1'-binaphthyl derivatives were shown to be effective catalysts for a variety of enantioselective transformations. In these compounds the rotation around the 1,1'-bond (connecting the two naphthyl systems) is sufficiently restricted for them to exist as non-planar rotamers, which are not superimposable. Instead they behave as mirror images of each other. These molecules are therefore chiral. This special form of stereoisomerism is called atropoisomerism and causes axial chirality.[41] Figure 16 shows the two enantiomers of this type.

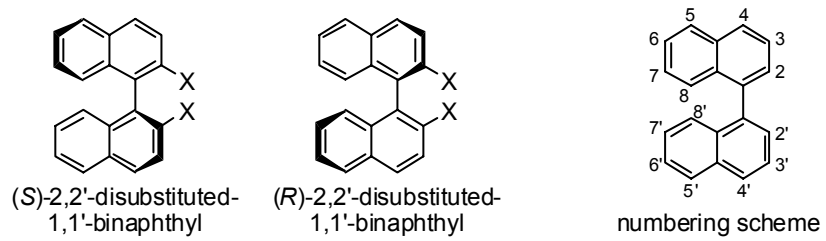


Figure 16. The two enantiomers of a binaphthyl derivative (the nomenclature of the absolute configuration depends on the nature of the substituents X; the (*R*) and (*S*) designations shown here hold for X substituents with higher priority then unbranched alkyl moieties). Shown to the right is the numbering scheme for binaphthyl derivatives.

As the stereochemistry in binaphthyl derivatives is defined solely by the *relative orientation* of the naphthyl moieties, racemization can occur by rotation around the 1,1'-bond. The rotational barrier of unsubstituted 1,1'-binaphthyl is 94 kJ/mol, corresponding to a half life of about 30 min at room temperature.[42] Bulky substituents in 2,2' position markedly increase the rotational barrier, while substituents in 8,8' position do so to a lesser degree. Substituents in other positions do not show significant influence on the rotational barrier.

Symmetrically substituted 1,1'-binaphthyls are C_2-symmetric, a desirable feature in many catalytic applications, since it reduces the number of possible diastereomeric transition states.[43]

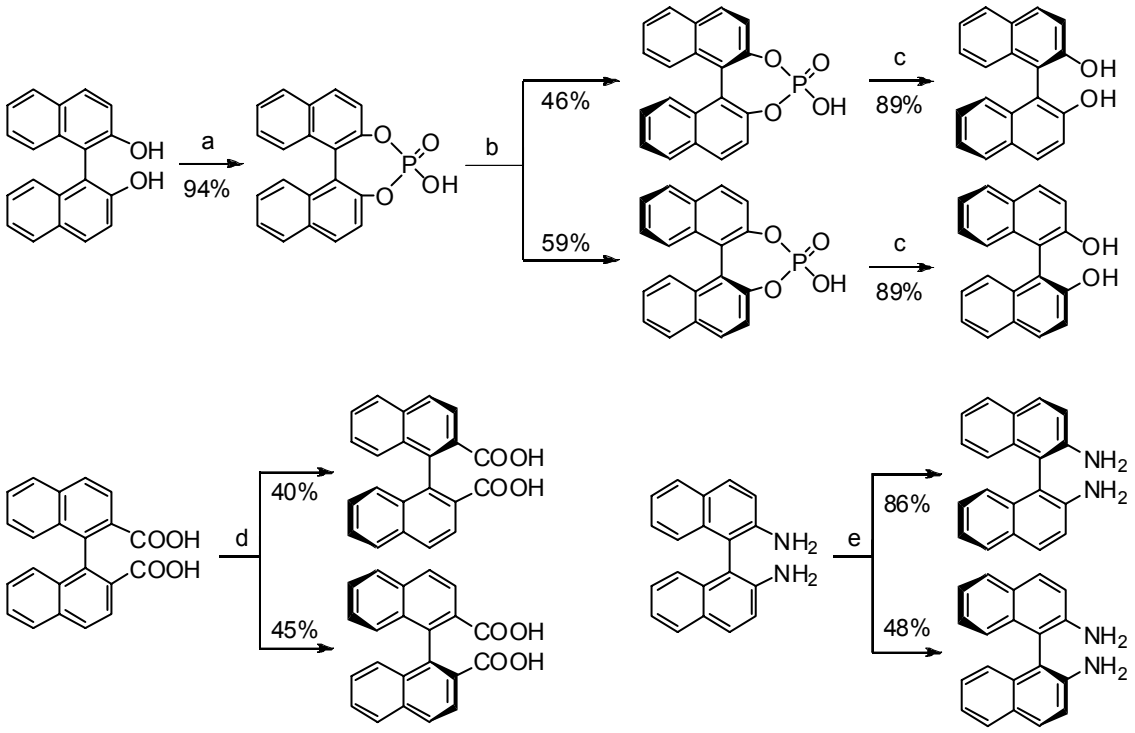
1.4.1 Nonracemic 1,1'-binaphthyl derivatives

The importance of binaphthyls in asymmetric catalysis poses the question of synthetic access to this compound class. Nonracemic 2,2'-disubstituted binaphthyls are available *via* a variety of methods. Subsequent derivatization is usually possible without loss of optical activity, due to the high rotational barriers around the 1,1'-axis (arising from the 2,2' substitution pattern). One exception is substituent exchange in 2,2' position, which poses a significant risk of racemization. Introduction or exchange of substituents in other ring positions and derivatization of the 2,2'-substituent are unproblematic though, and are indeed commonly employed. These strategies allow access to a wide variety of substituted 1,1'-binaphthyls.

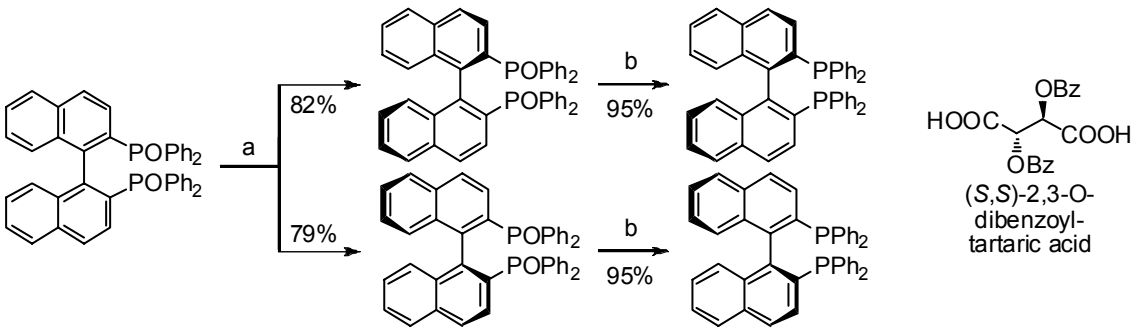
1.4.2 Synthesis of nonracemic 2,2'-disubstituted derivatives

As Putala has documented in his excellent review about nonracemic C_2-symmetric binaphthyls,[44] a large variety of methods for obtaining enantiopure 1,1'-binaphthyl derivatives is available: enantioselective oxidative or reductive couplings of 2-substituted naphthalenes, classical optical resolution of racemic 1,1'-binaphthyls, kinetic optical resolution,[45] *etc*.

Resolution is the most widely used method.[46] It offers facile access to both enantiomers, which is advantageous for catalytic applications. Common substrates for resolution are 1,1'-binaphthyl-2,2'-diol (BINOL),[46] 1,1'-binaphthtyl-2,2'-dicarboxylic acid[47] and 2,2'-diamino-1,1'-binaphthyl (DABN).[48] Resolution procedures for each of them are



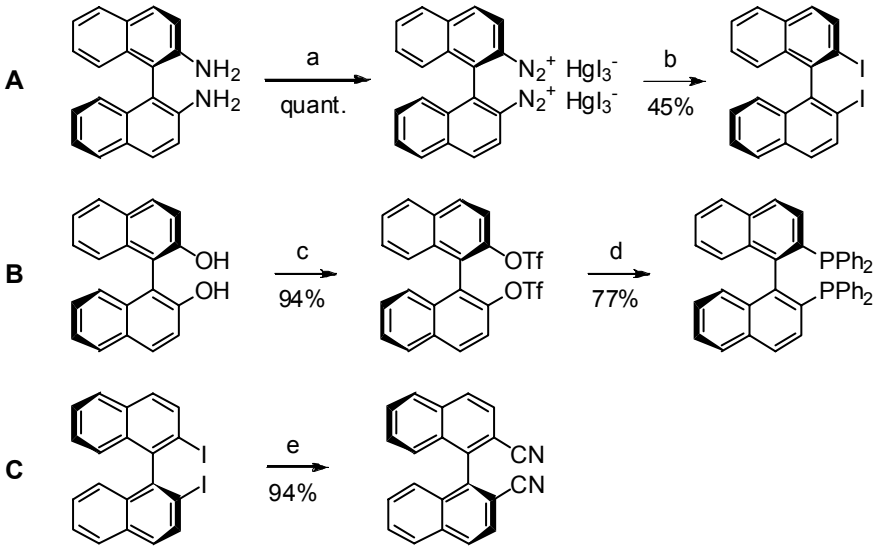
Scheme 2. Common resolution procedures for binaphthyls. Reagents and conditions: a) $POCl_3$, NEt_3, CH_2Cl_2, then H_2O/THF; b) cinchonine, MeOH/H_2O, then diastereomer separation, then EtOH, 6 M HCl aq.; c) $LiAlH_4$, THF, RT; then 6 M HCl aq.; d) brucine, acetone, methanol, then filtration of the precipitate followed by hydrolysis of precipitate and supernant; e) *d*-CSA, chlorobenzene, EtOH, 50 °C, then filtration of the precipitate followed by hydrolysis of precipitate and filtrate. (Bz = benzoyl, CSA =



Scheme 3. Synthesis of BINAP. Reagents and conditions: a) (*S*,*S*)-2,3-O-dibenzoyltartaric acid, EtOAc, $CHCl_3$, reflux, separation of the precipitate, then H_2O/NaOH; b) $HSiCl_3$, NEt_3. (Bz = benzoyl)

depicted in Scheme 2. Scheme 3 shows a resolution based synthesis of the important 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) ligand.[49]

Exchange of substituents in 2,2' position can be problematic, as (partial) racemization is frequently observed. Nevertheless, there are some reactions that proceed stereoconservatively, depending on the operating mechanism.

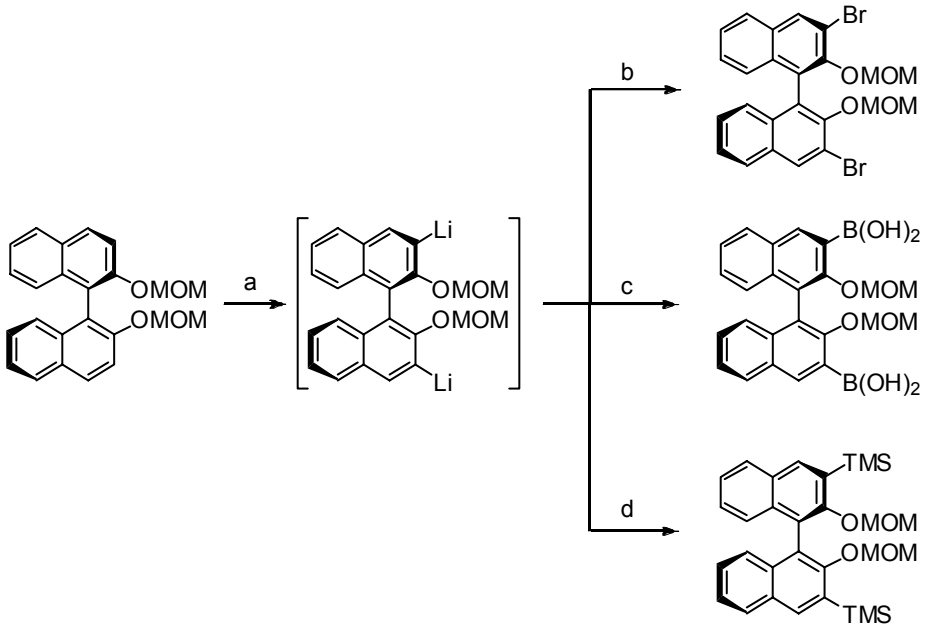


Scheme 4. Stereoconservative substitutions in 2,2' position. Reagents and conditions: a) H_2SO_4, $NaNO_2$, then water, $KHgI_3$; b) KI, 95 °C; c) TfOTf, pyridine, CH_2Cl_2; d) Ph_2PH, $NiCl_2$(dppe) cat., DMF, DABCO, 100 °C; e) $Zn(CN)_2$, $Pd(dppf)_2$ cat., DMF; 90 °C. (Tf = trifluoromethanesulfonate, dppe = 1,2-bis(diphenylphosphino)ethane, DMF = N,N-dimethylformamide, DABCO = 1,4-diazabicyclo[2.2.2]octane, dppf = 1,1'-bis(diphenylphosphino)ferrocene)

As Murdoch showed in 1985, diazotation of DABN, followed by decomposition of the diazonium salt in a KBr or KI matrix yields enantiopure 2,2'-dibromo-1,1'-binaphthyl (DBBN) and 2,2'-diiodo-1,1'-binaphthyl (DIBN), respectively (Scheme 4, A). While this procedure is frequently used for the synthesis of DIBN, its application for DBBN synthesis only seldom found in the literature. Classical Sandmeyer conditions result in considerable racemization.[50]

Substituent exchange in 2,2' position *via* transition metal catalyzed coupling reactions often proceed stereoconservatively. This has been applied to the synthesis of various 2,2'-disubstituted derivatives: dialkyl,[51] diaryl,[52] diferrocenyl[53] and dicyano[54] binaphthyls (Scheme 4, C). Also, a shorter route to BINAP has been reported *via* nickel catalyzed heterocoupling (Scheme 4, B).[55] Common starting materials for these reactions are DIBN or the bis(triflate), easily prepared from BINOL.

In contrast, substitution reactions in 2,2' position *via* lithium halogen exchange usually lead to racemization, due to the special structure of the dilithium intermediate (interaction of the lithium atoms with each other and/or the opposing binaphthyl moieties).[56] The rotational barrier of the dilithium compound was estimated as ~75-



Scheme 5. Application of directed *ortho*-metallation for the introduction of substituents in 3,3' position. Reagents and conditions: a) *n*-BuLi, TMEDA, Et_2O; b) $BrCl_2C$-CCl_2Br; c) $B(OEt)_3$, then water; d) TMS-Cl. (MOM = methoxymethyl, TMS = trimethylsilyl, TMEDA = N,N,N',N'-tetramethylethylenediamine)

80 kJ/mol.[57] Some limited successes have been reported though, usually requiring inconvenient solvents or carefully controlled reaction conditions.[58]

1.4.3 Substituents in other positions

Electrophilic aromatic substitution at activated 1,1'-binaphthyls preferentially occurs in 6,6' position. While this pattern is seldom useful for chiral catalysis applications, it was shown to be viable for nonlinear optics materials.[59]

Directed *ortho*-metallation of suitable 2,2'-disubstituted binaphthyls allows introduction of substituents in 3,3' position. This synthetic approach has found widespread use, as 3,3'-substituents can strongly interact with the catalytic center. The most widely used substrates for *ortho*-metallations are O-protected BINOLs.[60] The large number of available electrophiles allows facile introduction of synthetically valuable substituents: for example iodide, bromide, boronic acid and trimethylsilyl.

The trimethylsilyl group is a convenient synthetic handle for *ipso*-substitution, allowing for example introduction of other halogens.

The boronic acid functionality on the other hand can be oxidized to introduce hydroxy groups,[61] which can be used to immobilize the compounds on a resin or to attach perfluorous alkyl chains to modify solubility properties. Alternatively, the boronic acid

can be used in Suzuki cross coupling reactions to introduce aryl substituents.[62] The broad scope of the Suzuki reaction makes boronic acid substituents in 3,3' position a particularly valuable synthetic handle.

Likewise, halogen substituents, in particular iodine and bromine are of interest, as they can be used to introduce further substituents *via* a wide range of reaction classes: transition metal catalyzed coupling reactions, lithium halogen exchange, *etc*. Especially the former are of eminent practical importance, as they provide access to aryl-, alkene-, alkyne-,[63] allyl-,[64] cyano-[65] and amino[66] substituted binaphthyls.

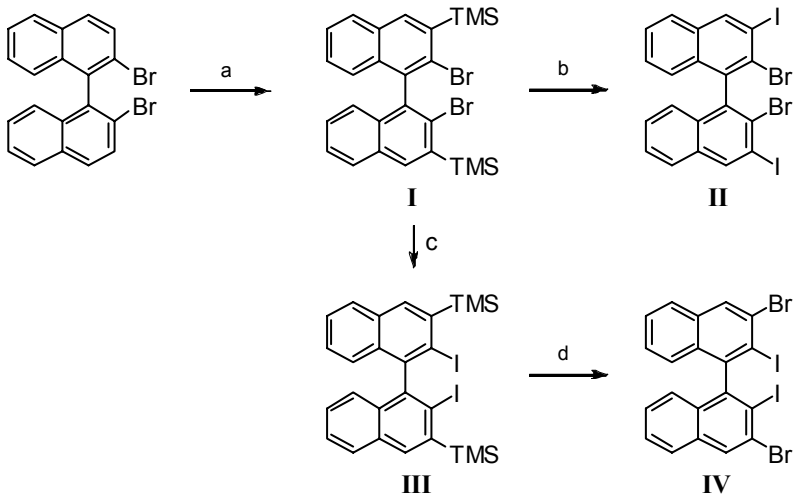
1.5 Aim and scope of this thesis

The initial goal was to show the validity of a synthetic approach to C_2 symmetrical 2,2',3,3'-tetrasubstituted binaphthyls devised by M. Widhalm. This method had already been applied to the synthesis of some exemplary compounds, but further investigations were necessary to demonstrate scope and limitations.

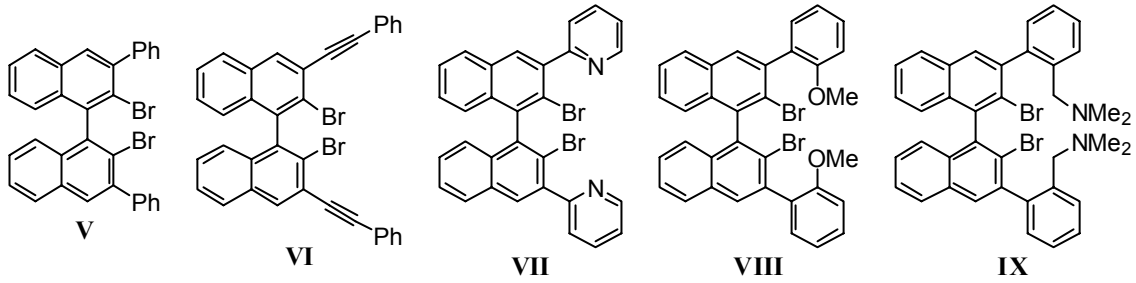
During these studies the need for enantiopure DBBN arose. After some experimentation with published procedures, a new synthetic approach was devised, which promised better yields and more reproducible enantiomeric excesses.

The following sections give a more detailed overview.

1.5.1 A novel approach to 2,2',3,3'-tetrasubstituted binaphthyl compounds



Scheme 6. Synthesis plan for dibromodiiodobinaphthyls. Reagents: a) LiTMP, TMSCl; b) ICl; c) *n*-BuLi, I_2; d) NBS. (TMS = trimethylsilyl; TMP = tetramethylpiperidine; NBS = N-bromosuccinimide).

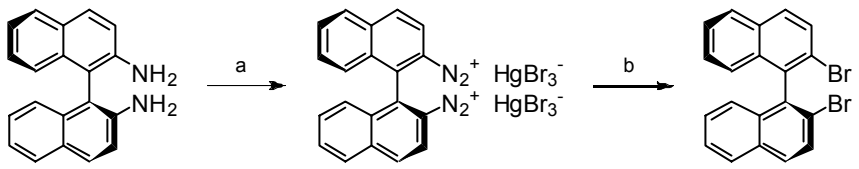


Scheme 7. Some exemplary derivatives of **II**.

As shown in the previous sections, the most common route to 2,2',3,3'-tetrasubstituted binaphthyls is *ortho*-metallation of O-protected BINOLs. While this method works well and is indeed quite popular, the exchange of the hydroxyl moiety in 2,2' position later on is troublesome. *Ortho*-metallation of N-protected DABN compounds was demonstrated as recently as 2006.[67] Previously 3,3'-substituted DABN derivatives were only accessible by coupling of appropriately substituted naphthalenes. BINAP derivatives with additional substituents in 3,3' position have been reported, but were synthesized in a cumbersome way starting from 1-bromo-3-hydroxynaphthalene.[68] Reports of tetrasubstituted binaphthyls with other heteroatoms in 2,2' position are scarce. Therefore, a new and flexible synthetic approach to C_2 symmetric 2,2',3,3'-tetrasubstituted binaphthyls was sought.

Dibromodiiodobinaphthyls **II** and **IV** were thought to be useful synthetic intermediates, allowing selective introduction of substituents in 2,2'- and 3,3' position through exploitation of the reactivity differences between iodine and bromine. DBBN was deemed a viable precursor, permitting facile introduction of a trimethylsilyl substituent in 3,3' position *via* directed *ortho*-metallation,[69] which can be further elaborated into a bromine or iodine substituent. Exchange of the halogen in 2,2' position seemed possible *via* lithium halogen exchange. Scheme 6 shows the envisaged reaction sequence.

The dibromodiiodobinaphthyls **II** and **IV** should provide access to a large variety of



Scheme 8. Devised synthetic approach to DBBN. Reagents and conditions: a) H_2SO_4, $NaNO_2$, then water, $KHgBr_3$; b) hν, KBr, no solvent.

derivatives. The focus was on **II**, especially on the introduction of new substituents in 3,3' position, mainly *via* transition metal catalyzed cross coupling reactions. Compounds **V**-**IX** were planned to be synthesized this way (Scheme 7).

Further elaboration of these compounds by lithium halogen exchange should also be viable; this was to be demonstrated with the introduction of iodine. Alternatively, transition metal catalyzed reactions could be used, although the steric hindrance may pose a problem.

1.5.2 Synthetic studies towards enantiopure 2,2'-dibromo-1,1'-binaphthyl

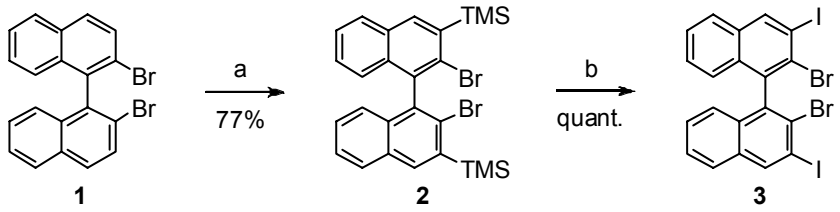
It should be noted that in the previous section, compounds **I**-**X** could be obtained in nonracemic form if enantiopure DBBN was used as starting material. While performing studies in this vein, we tried several known procedures for the synthesis of DBBN and finally decided to investigate alternative routes in order to obtain better yields and better reproducibility of the enantiomeric excess of the product.

A different method for decomposition of diazonium salts was published in 1961, reporting the use of UV light. Preliminary tests on small scale with the bis(diazonium) tribromomercurate showed the viability of this approach (Scheme 8, step b), thus more thorough investigations in this vein were deemed worthwhile.

2 Results and discussion

2.1 Synthetic approaches to racemic 2,2',3,3'-tetrasubstituted binaphthyls

The synthesis of 2,2',3,3'-tetrasubstituted binaphthyls started from commercially available 2,2'-dibromo-1,1'-binaphthyl (**1**). Directed *ortho*-metallation in the presence of trimethylsilyl chloride yielded **2**, which was converted to **3** via *ipso*-substitution (Scheme 9).

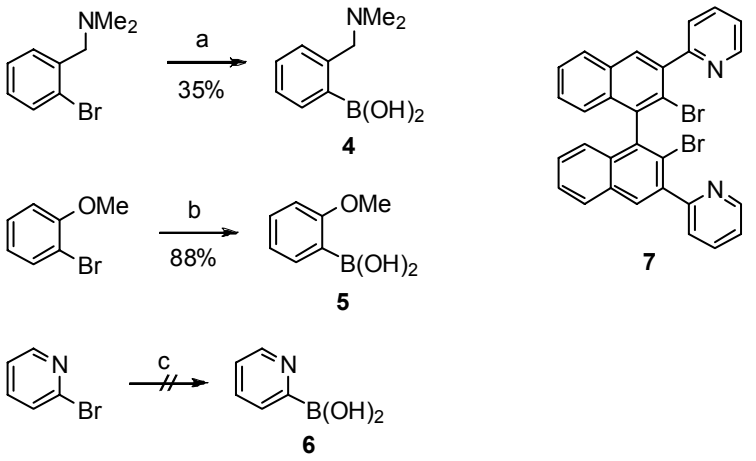


Scheme 9. Reagents and conditions: a) Li-TMP, THF, –78 °C, then TMS-Cl, –78 °C to RT; b) ICl, CH_2Cl_2, –40 °C. (Li-TMP = lithium tetramethylpiperidide, TMS = trimethylsilyl)

The enhanced reactivity of iodides compared to bromides in transition-metal catalyzed cross coupling reactions, together with steric factors, allowed **3** to be regioselectively derivatized (Table 1). In all coupling reactions performed, only substitution in 3,3' position was observed. As to be expected, the predominating C_2-symmetrical products were usually accompanied by C_1-symmetrical side products where only single substitution had taken place. Those byproducts formed in only minor amounts and were easily removed by flash chromatography.

Especially the Suzuki coupling reaction was thought to allow access to a wide variety of products. The required boronic acids were mostly obtained from commercial sources, only **4** and **5** had to be prepared according to known literature procedures: Directed *ortho*-metallation of benzyldimethylamine followed by quenching with trimethyl borate yielded **4**.[70] The reaction of the Grignard reagent derived from 1-bromo-2-methoxybenzene with trimethyl borate afforded **5**.[71]

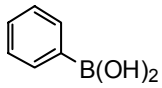
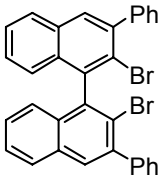
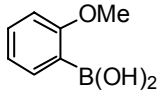
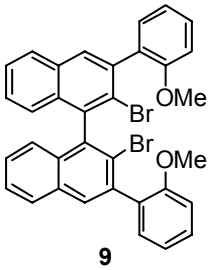
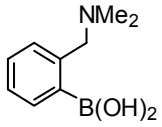
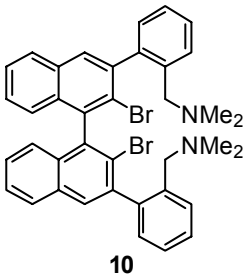
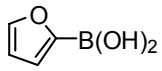
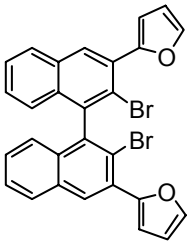
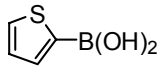
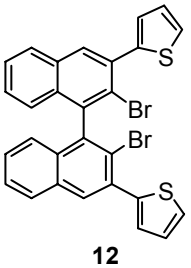
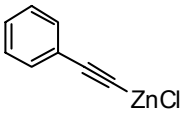
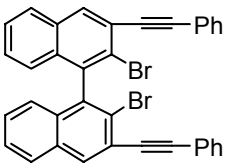
Preparation of the pyridylboronic acid **6** was also planned, however the procedure[72] reported in the literature could not be reproduced. Upon workup only an insoluble, white substance was obtained which did not match the physical and spectroscopic properties given in the literature.[72] A different route to the desired binaphthyl derivate **7** was chosen instead, avoiding boronic acid **6** (see below).



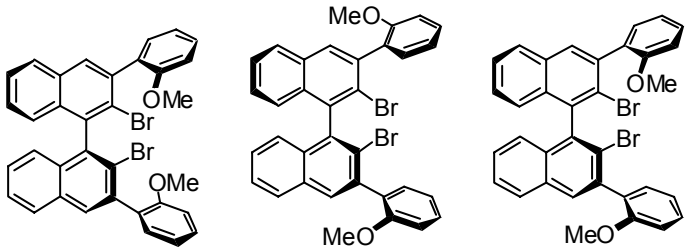
Scheme 10. Reagents and conditions: a) *n*-BuLi, TMEDA, Et_2O, RT, 8 h, then $B(OMe)_3$, –78 °C to RT, 24 h; b) Mg, THF, reflux, then $B(OMe)_3$ in THF, –78 °C to RT, 8 h; c) iPrMgCl, THF, 1 h, then $B(OTMS)_3$, 0 °C to RT, 8 h. (TMEDA = N,N,N',N'-tetramethylethylenediamine)

Suzuki coupling was shown to be a viable way of introducing aromatic moieties, yielding compounds **8-12**. Both, thermal and microwave conditions worked, the latter giving much faster but not always better results. While reactions with homoaromatic boronic acids were usually successful, coupling with heteroaromatic boronic acids proved troublesome. Frequently, screening of reaction conditions was necessary to obtain reasonable results. A common phenomenon was black precipitate of Pd(0) in reaction mixtures, which pointed to instability of the catalyst under the applied conditions.

Table 1. Products **5-10** prepared by palladium catalyzed couplings of **3**[a]

Coupling partner	Conditions	Product	Yield (%)
	a	 **8**	80
	c		90
 **5**	b	 **9**	41
	c		75
 **4**	c	 **10**	0[b]
	b	 **11**	12
	b	 **12**	61
 **13**	d	 **14**	85

[a] Reagents and conditions: a) $Pd(PPh_3)_4$, Na_2CO_3 aq., toluene, µw; b) $Pd(PPh_3)_4$, Na_2CO_3 aq., DME, µw; c) $Pd(PPh_3)_4$, Na_2CO_3 aq., toluene, 105 °C; d) $Pd(PPh_3)_4$, THF, 65 °C. [b] Product not recovered after flash chromatography; cf. running text.



9a **9b** **9c**

Figure 17. The three diastereomeric rotamers of **9**. While **9a** and **9b** are C_2 symmetric, **9c** has C_1 symmetry.

Unexpectedly, NMR studies revealed that **9** was isolated as a mixture of rotamers, quickly interconverting at room temperature. While bromo substituents exert sufficient steric interaction to fully prevent rotation around the binaphthyl axis, the two methoxy groups are too small to completely eliminate rotation around the phenyl-naphthyl axis. Because of the presence of three stereogenic elements, formally 4 diastereomers should be expected; in practice, two of those have the same three-dimensional structure due to rotational symmetry. Consequently one C_1 symmetric and two C_2 symmetric rotamers are found, along with their respective enantiomers (Figure 17).

On the NMR timescale, four overlapping methoxy peaks were observed at RT, indicative of the presence of all three possible rotamers. Deconvolution of the overlapping peaks showed that all three compounds are present in nearly equal amounts; consequently there can only be a minute energy difference between the isomers.

Spectra recorded at different temperatures between 300 and 360 K showed coalescence, and a clean averaged spectrum with the expected C_2 symmetry and a single methoxy peak was observed at 360 K. Assignment of the individual peaks in the low temperature spectra was not possible, which made an estimation of isomerization kinetics difficult. A further complication was the presence of 3 different substances in the equilibrium. From the shift differences and coalescence temperature T_c, the free activation enthalpy was found to be in the range of 69.5 ± 1 kJ/mol (between 310 and 325 K), independent of the chosen peak assignment. The data suggest that the isomerization half life is on the order of 10 ms at 325 K.

Since the usefulness of a rotameric mixture for catalytic applications seemed highly doubtful, work on this compound was abandoned.

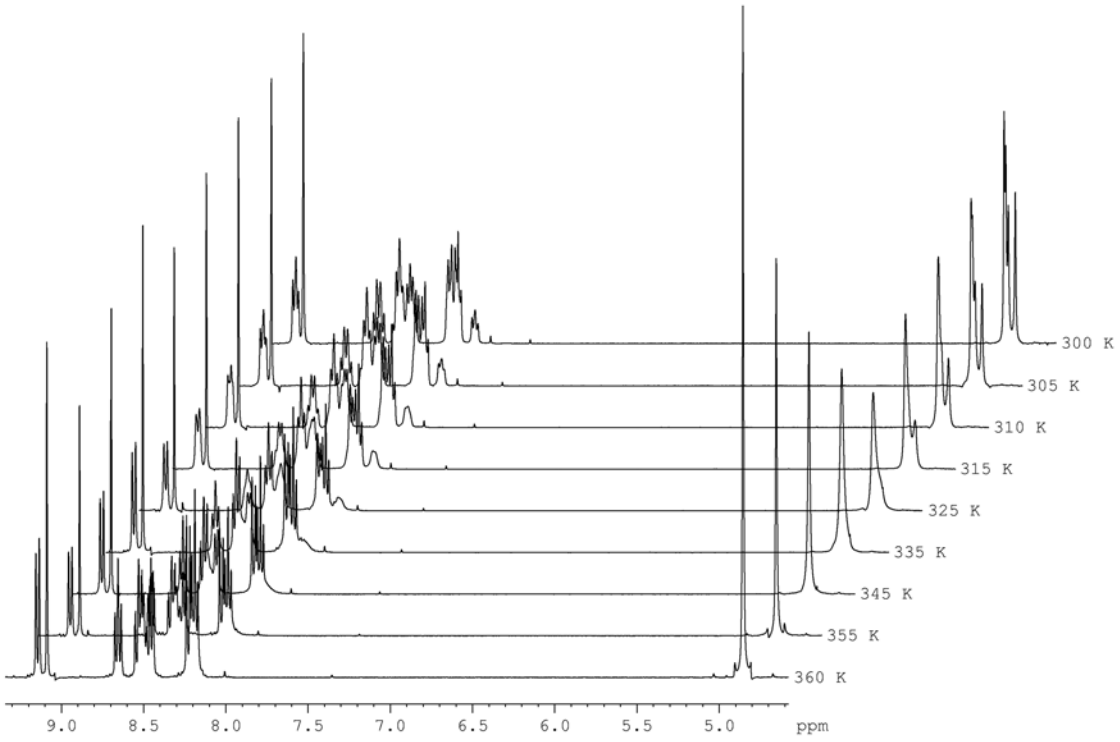


Figure 18. ^{1}H-NMR spectra of **9** in DMSO-d_6 at different temperatures. Peak coalescence with rising temperature is most easily seen for the methoxy peak at 4.9 ppm.

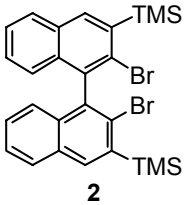
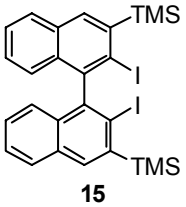
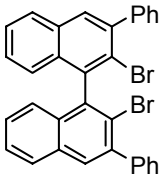
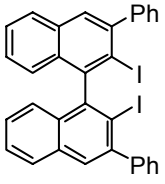
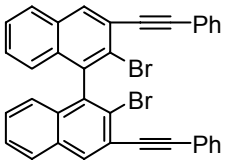
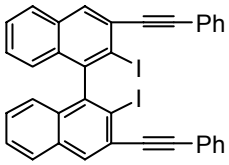
Compound **10** was obtained in crude form *via* Suzuki coupling but could not be recovered after flash chromatography on silica. As it seemed likely that **10** would, like **9**, be a mixture of rotamers, this was not investigated further.

Suzuki coupling also allowed introduction of heteroaromatic moieties, such as furyl and thienyl groups, yielding **11** and **12**, respectively. Forcing conditions were required though: with conventional heating no product could be isolated. Under microwave irradiation with DME as solvent,[73] products were formed, though there were stability problems related to the catalyst; Pd(0) precipitation was frequently observed. As a result, the obtained yields were relatively low.

Negishi coupling of **3** with the organozinc compound **13** prepared *in situ* from ethynylbenzene gave **14** in good yield, as had already been reported for a related compound.[63]

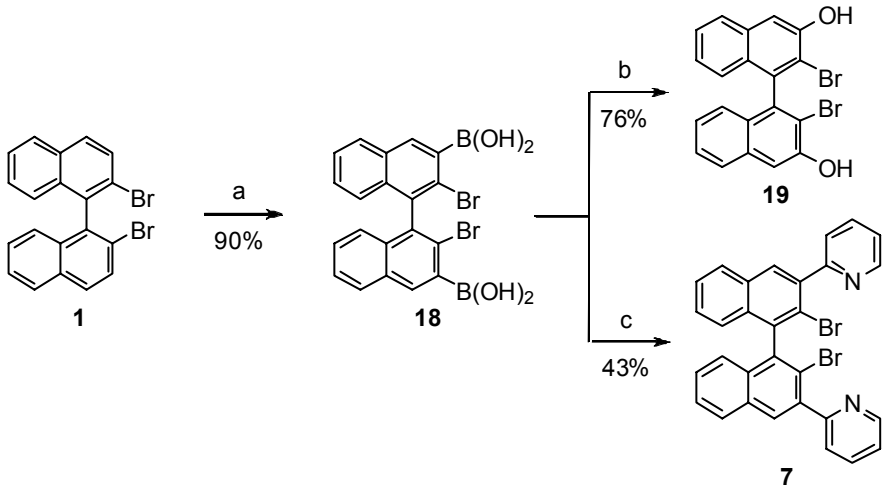
To demonstrate the possibility of further functionalization *via* lithium halogen exchange, compounds **15-17** were synthesized by treating **2**, **8** and **14** with *n*-butyllithium and quenching with iodine. The results are summarized in Table 2.

Table 2. Introduction of iodide substituents by lithium halogen exchange.[a]

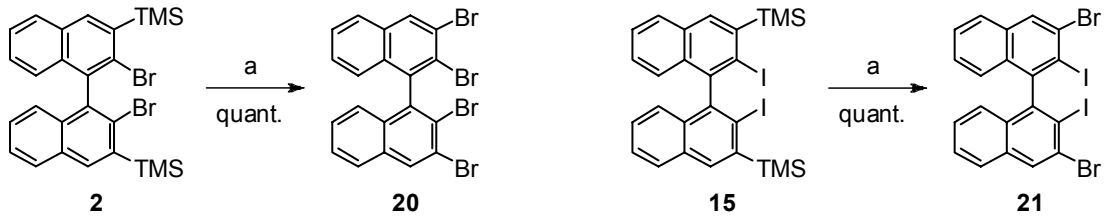
Starting material	Product	Yield (%)
 **2**	 **15**	quantitative
 **8**	 **16**	87
 **14**	 **17**	33

[a] Reagents and conditions: *n*-BuLi, THF, –78 °C, 1 h, then I_2, –78 ° C to RT.

A different approach for introduction of substituents in 3,3' position was also tried: directed *ortho*-metallation of **1** followed by quenching with triisopropyl borate. After hydrolysis, boronic acid **18** was obtained. Since purification by flash chromatography proved difficult, the crude product (obtained after acid/base workup) was used for further reactions.

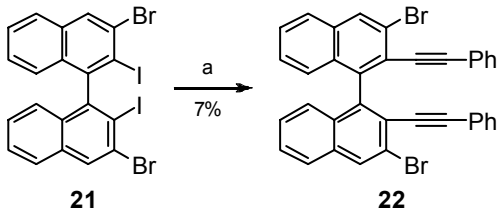


Scheme 11. Reagents and conditions: a) Li-TMP, THF, –78 °C, $B(OiPr)_3$, –78 °C to –45 °C, cooling back to –78 °C, $B(OiPr)_3$, –78 °C to RT; b) H_2O_2; c) 2-bromopyridine, $Pd(PPh_3)_4$, Na_2CO_3. (Li-TMP = lithium tetramethylpiperidide)



2 **20** **15** **21**

Scheme 12. Reagents and conditions: a) NBS, acetonitrile, RT, 8 h. (TMS = trimethylsilyl, NBS = N-bromosuccinimide)



21 **22**

Scheme 13. Reagents and conditions: a) **13**, $Pd(PPh_3)_4$, THF, 65 °C.

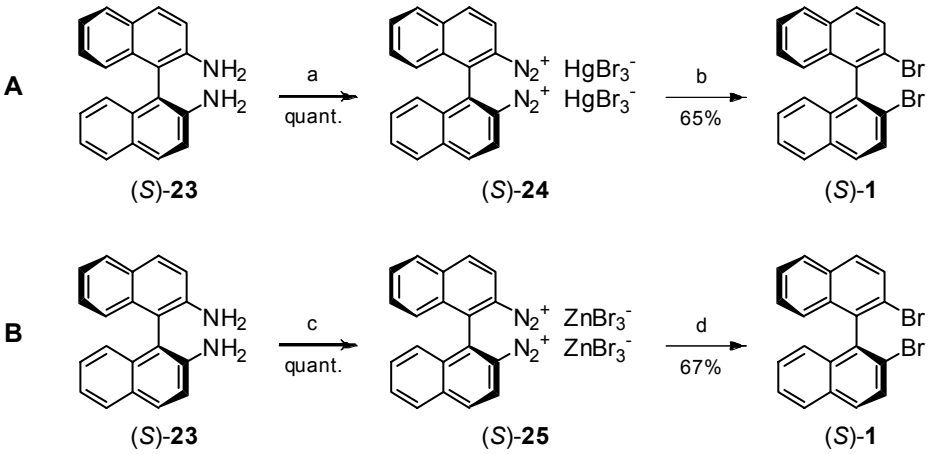
Oxidation with H_2O_2 afforded **19**, while Suzuki coupling allowed introduction of pyridyl substituents in 3,3' position to yield **7**, which was not accessible *via* coupling of **3** (as the requisite pyridylboronic acid **6** could not be obtained; cf. p. 19). Scheme 11 summarizes the synthetic route.

Further, compounds **20** and **21** were synthesized (Scheme 12). *Ipso*-substitution of the trimethylsilyl group for bromide worked well with N-bromosuccinimide (NBS) in acetonitrile. To the best of my knowledge, this reagent/solvent system was not previously known for displacement of TMS groups on aromatic rings. The conditions were adapted from a publication about bromination of methoxybenzenes.[74]

Subsequently, **21** was used in a Negishi cross coupling with reagent **13**, which furnished **22** (Scheme 13), but only in poor yield and together with numerous side products. This result can be understood by considering the competition between electronic and steric influences.

2.2 Synthetic studies towards enantiopure 2,2'-dibromo-1,1'-binaphthyl

As mentioned above, the previously discussed reactions would likely yield enantiopure binaphthyls if the synthesis started from a single enantiomer of **1**. Nonracemic **1** is available commercially, but is expensive. However, it can be synthesized starting from



Scheme 14. Murdoch's and Hagiwara's approaches to enantiomerically pure **1**. Reagents and conditions: a) H_2SO_4, $NaNO_2$, –5 °C, then KBr/$HgBr_2$; b) KBr, vacuum, 95 °C; c) H_2SO_4; $NaNO_2$; –5 °C, then KBr/$ZnBr_2$; d) cyclohexane, reflux.

amine **23**, either *via* Murdoch's procedure[75] (Scheme 14, A) or using Hagiwara's modified conditions[76] (Scheme 14, B).

Hagiwara's approach was tried first, and the synthesis of diazonium salt **25** worked in good yields. Unfortunately, the decomposition to yield **1** gave poor results in my hands. Following the preparation, **25** was ground with KBr, and the mixture was dried thoroughly. Subsequently, the solids were refluxed in cyclohexane. Every hour, the supernatant was decanted and fresh cyclohexane was added. The decanted solvents were evaporated separately to yield **1**. Enantiomeric excesses were determined by chiral HPLC. Table 3 shows the results: the yield was generally low, and the ee was decreasing with each batch of solvent. Combining all batches, the yield did not exceed 20 %, and the ee was only 85 %.

Table 3. Batches of nonracemic **1** collected following Hagiwara's method: yields were very low and the ee decreased rapidly as the reaction progressed.

Batch[a]	Yield (%)	ee (%)
1	9	95
2	8	80
3	3	75
Sum	20	85

[a] Product batches obtained by decanting and evaporating cyclohexane supernatants every hour.

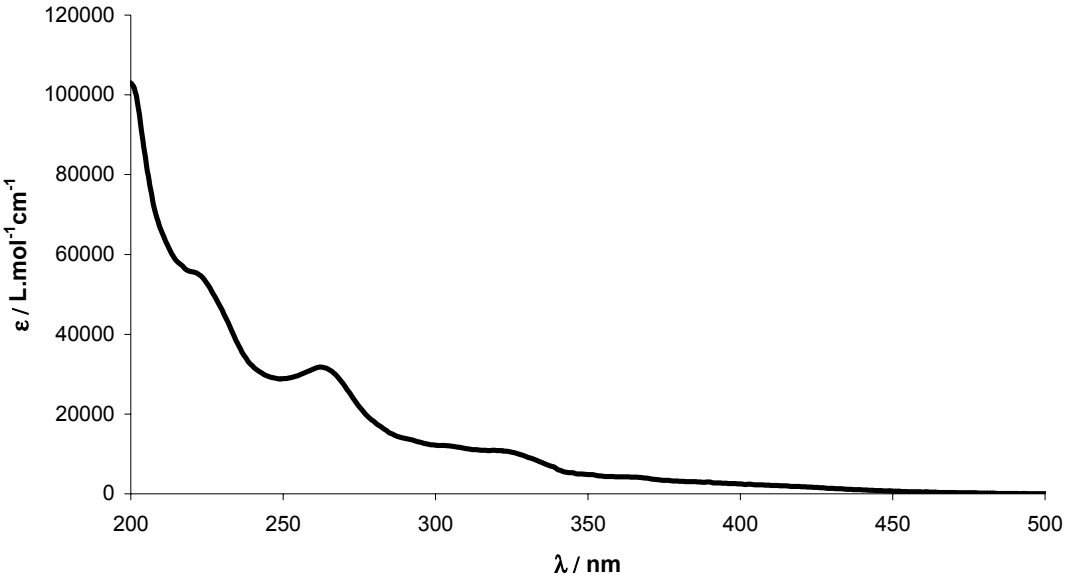


Figure 19. This UV/VIS spectrum of **24** clearly shows a broad absorption peak centered at 319 nm, which is absent from the spectrum of 1,1'-binaphthyl.[78]

After this setback, attention turned to Murdoch's procedure. Again, synthesis of the diazonium salt **24** worked well. After grinding **24** with KBr and drying, the solids were heated to 95 °C under vacuum (< 1 torr) for 20 min. After workup, **1** was obtained in 57 % yield, but with only 87 % ee.

As the synthesis of **24** and **25** worked well, alternative methods for decomposition of diazonium salts were sought. Extensive literature searching showed that UV irradiation can effect this transformation.[77]

The UV/VIS spectrum of **24** (Figure 19) and **25** did indeed show the presence of a distinctive peak at 319 nm which was not present in similar binaphthyl compounds. Following this insight, small scale experiments with a TLC detector lamp were conducted. A mixture of KBr and **24** was irradiated a) dry, b) in pentane, c) in acetone and d) in a water/bromine mixture. While only analytical quantities of **1** were obtained, the observed enantiomeric excesses in the dry and the pentane reaction (93-95 %) were encouraging. In acetone no product was formed, and the reaction in water/bromine gave inferior ee. Unfortunately, irradiation of the less toxic **25** gave no product.

Subsequently, several different lamps were surveyed. For larger preparations, the best results were achieved with a "Heraeus TQ718-Z4" medium pressure mercury lamp (700 W, doped with FeI_2, Pyrex® filter), whose main feature was high photon output in

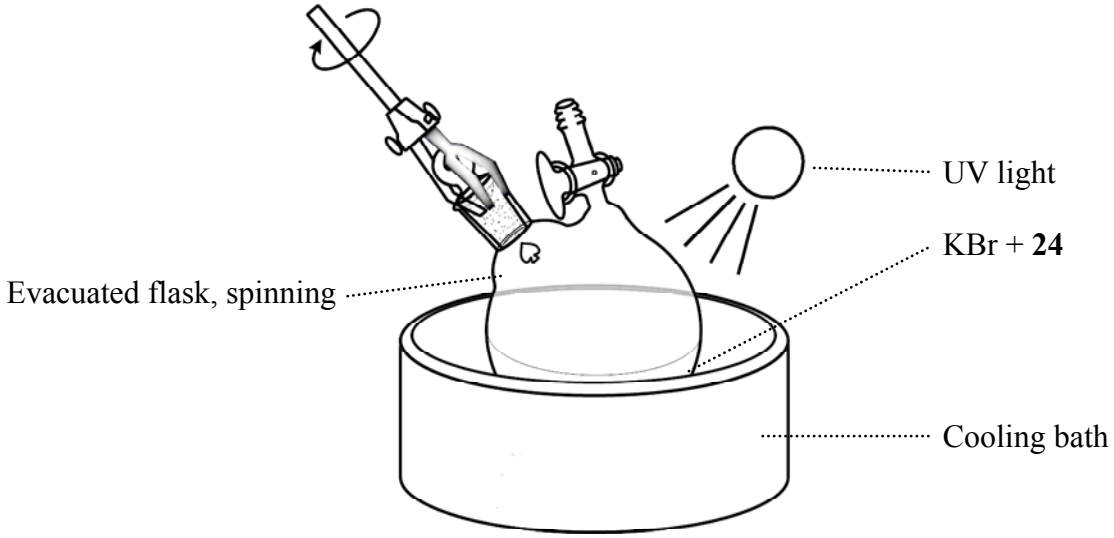
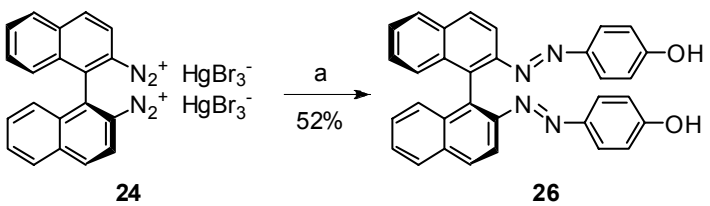


Figure 20. Schematic drawing of the photolysis setup.

the desired spectral region. Fortunately, reactions could be performed in normal Pyrex glassware; the UV cutoff at 280 nm did not prove problematic.

Investigations showed that best enantiomeric purity was attained if the reaction was run without solvent and with a large excess (~ 30 times the weight) of KBr as matrix. Performing the transformation at low temperature (–78 °C) and under vacuum (~1 torr or less) also had a positive effect. The apparatus used is depicted in Figure 20.

To determine whether partial racemization might occur during diazotation, a method for analyzing the enantiomeric purity of **24** was necessary. Since the diazonium salt itself was too unstable for analysis *via* chiral GC or HPLC, it had to be derivatized. Azo coupling with phenol under basic conditions in methanol yielded **26** (Scheme 15, Figure 21), which could be readily analyzed by chiral HPLC. The resulting data confirmed that enantiomeric purity was indeed lost during synthesis of **24**: several different batches were analyzed, and the ee's were consistently in the range of 96-98 %, while for the precursor (*S*)-**23** only a single enantiomer could be detected. Unfortunately, this amount of racemization could not be avoided in all of the performed experiments.



Scheme 15. Reagents and conditions: a) phenol, NaOH, methanol, RT, 1 h.

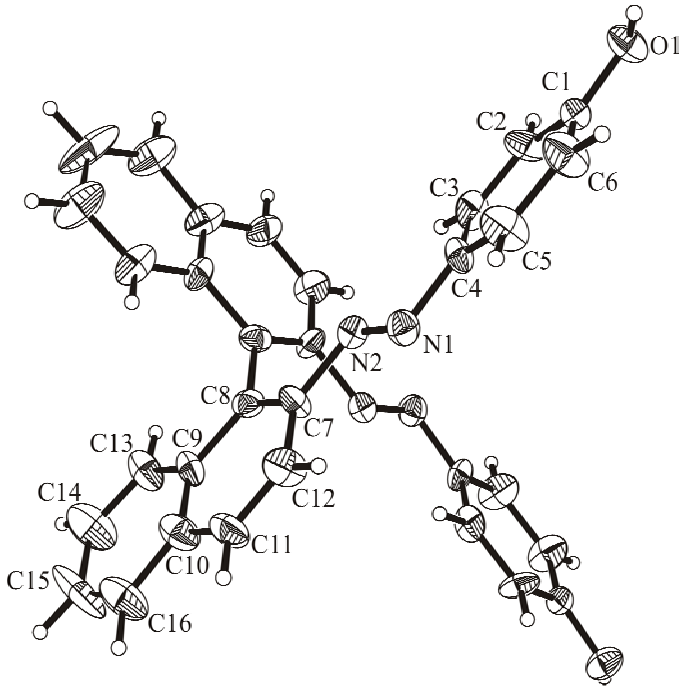


Figure 21. ORTEP visualization of **26**; data obtained *via* single crystal X-ray diffraction.

Longer storage of **24** at +10 or –20 °C did not further impact the ee of the diazonium salt. However, it was observed that the dry diazonium salt slowly decomposed even at low temperature, and that the thus formed **1** had only about 80-90 % ee. Consequently, it is advisable to thoroughly wash **24** with ether after prolonged storage; otherwise already formed **1** would negatively affect the ee of the final product. This finding should hold true, independent of the method for decomposition of **24**.

One recurring problem in the photolysis reaction was ensuring adequate mixing of the solids during irradiation. Due to the large density of the mixture, stir bars tended to float on the surface, which greatly reduced their effect. That difficulty was further aggravated by the tendency of finely ground **24** to form lumps. To overcome these troubles, two approaches were used: 1) during the reaction, the flask itself was spun to ensure adequate mixing, and 2) coarse KBr was added to the solids prior to irradiation to make the mass more freely flowing. These two techniques mostly eliminated the problem of unreacted chunks of starting material.

One major drawback of the photochemical appraoch described here is the need for a stoichiometric amount of photons, since the solvent-free conditions make chain reactions impossible. The relatively low extinction coefficient ε of **24** at the required

wavelengths corroborates this issue. Accordingly, long irradiation times are required, which is especially problematic in light of the low temperatures required.

Nevertheless, large amounts of **1** were synthesized using this technique. Typically material with about 94 % enantiomeric excess was obtained. Chemical yields were also good: up to 90 %. Lower yields were sometimes seen, mainly if the reaction was stopped too early. A good indicator for reaction progress is the color of the solids. Yellow at first, it changes to a grayish pink upon completion. Prompt inspection is necessary, though, as the color tends to fade upon warming.

Manual shaking of the reaction mixture might be used to reveal chunks of unreacted yellow starting material. Once no more yellow material surfaces on shaking, the reaction can usually be considered complete.

A number of mechanistic questions remain open: for example, whether an ionic or a radical pathway predominates. Accurate predictions are challenging, since several distinct mechanisms have been reported for similar reactions.[79] In addition, published investigations focusing on UV initiated dediazotations are scarce. Consequently, further experiments are needed to address these issues.

3 Experimental section

^{1}H and ^{13}C spectra were recorded on a Bruker „Avance DPX 400“ at 400 MHz and 100 MHz, respectively. ^{13}C spectra were recorded in a *J*-modulated mode; signals are assigned as C, CH, CH_2 or CH_3. Chemical shifts δ are reported in ppm relative to the residual peaks of the deuterated solvent used. Spectra recorded in $CDCl_3$ are referenced to 7.24 (^{1}H) and 77.00 (^{13}C), spectra recorded in methanol-d_4 to 3.31 (^{1}H) and 49.00 (^{13}C) ppm; spectra recorded in DMSO-d_6 to 2.50 (^{1}H) and 39.52 (^{13}C).

EI-MS (50 eV or 70 eV) or ESI-MS determinations were carried out on a Finnigan MAT 8230 spectrometer. HRMS determinations were carried out on a Finnigan MAT 8230 spectrometer.

Melting points were determined with a Reichert Thermovar melting point microscope and are uncorrected.

Microwave reactions were carried out in a MLS “Start 1500” microwave laboratory system in capped vials.

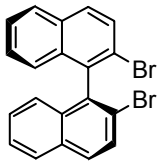
Analytical thin layer chromatography (TLC) was carried out on Merck “TLC Silica Gel 60 F_{254}” plates; UV (254 nm) was used for visualization. The silica gel used for preparative flash chromatography was “Silica gel 60 M” (40-63 μm) obtained from Macherey-Nagel.

For reactions under water-free conditions, oven-dried glassware was used and the reaction was performed under argon. Where noted, the reaction mixtures were degassed by three freeze-pump-thaw cycles.

PE, CH_2Cl_2 and EtOAc were distilled, THF was dried by distillation from sodium/benzophenone ketyl. Unless otherwise noted, *n*-butyllithium was used as 1.6 M solution in hexanes, $ZnCl_2$ as 1 M solution in THF. Tetrakis(triphenylphosphine)palladium(0),[80] racemic 2,2’-dibromo-1,1’-binaphthyl (**1**),[50] 2-((dimethylamino)methyl)phenylboronic acid (**4**)[70] and 2-methoxyphenylboronic acid (**5**)[71] were prepared according to published procedures. All other chemicals were used as received.

3.1 (S)-2,2'-Dibromo-3,3'-bis(trimethylsilyl)-1,1'-binaphthyl ((S)-1)[i]

3.1.1 Preparation



KBr (33.3 g, 280 mmol) and (*S*)-**24** (1.0 g, 0.84 mmol) were thoroughly ground, then coarse KBr (10 g, 84.1 mmol) was added to make the mixture less sticky. The solids were transferred into a Schlenk flask which was evacuated, cooled to –78 °C, and placed under UV light (Heraeus "TQ718-Z4" medium pressure mercury lamp). When no more yellow chunks were visible (~9 h), the solids were extracted with CH_2Cl_2 (4 × 50 mL). The combined solvents were evaporated and the crude product was purified by flash chromatography (silica gel, PE) to give (*S*)-**1**.

Yield: 268 mg (77 %).

3.1.2 Analytical data

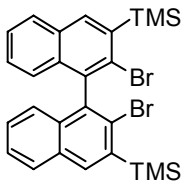
^{1}H-NMR ($CDCl_3$) δ 7.92 (2H, d, J = 8.2 Hz), 7.86 (2H, d, J = 8.8 Hz), 7.80 (2H, d, J = 8.8 Hz), 7.48 (2H, ddd, J = 8.2, 6.9, 1.2 Hz), 7.29 (2H, ddd, J = 8.4, 7.0, 1.4 Hz), 7.08 (2H, d, J = 8.5 Hz).

^{13}C-NMR ($CDCl_3$) δ 137.10 (C), 133.30 (C), 132.36 (C), 129.97 (CH), 129.77 (CH), 128.23 (CH), 127.37 (CH), 126.33 (CH), 125.83 (CH), 122.71 (C).

[i] For the preparation of racemic **1**, see ref. 50.

3.2 2,2'-Dibromo-3,3'-bis(trimethylsilyl)-1,1'-binaphthyl (2)

3.2.1 Preparation



Dry THF (75 mL) was added to 2,2,6,6-tetramethylpiperidine (15.3 mL, 12.71 g, 90 mmol) and the solution was degassed. After cooling to 0 °C under argon, *n*-butyllithium (2.5 M in hexanes, 36.0 mL, 90 mmol) was added dropwise over ~10 min. After 30 min stirring at 0 °C the solution was cooled to –78 °C and trimethylsilylchloride (19.0 mL, 16.30 g, 150 mmol) was added. The solution was stirred for further 20 min at –78 °C. A solution of **1** (6.18 g, 15 mmol) in THF (50 mL) was degassed, cooled to –78 °C and slowly added *via* Teflon cannula. Careful temperature control during the addition was necessary to achieve good yields. The solution was then allowed to warm to RT overnight.

The reaction mixture was cooled to 0 °C and quenched with HCl aq. (2 M, 150 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with H_2O (1 × 100 mL) and NaCl aq. sat. (1 × 100 mL) and dried over $MgSO_4$. The solvents were pulled off and the crude product was purified by flash chromatography (silica gel, PE), affording **2** as a white foam.

Yield: 6.45 g (77 %).

3.2.2 Analytical data

mp 152-154 °C ($MeOH/Et_2O$).

^{1}H-NMR ($CDCl_3$) δ 8.07 (2H, s), 7.90 (2H, d, J = 8.1 Hz), 7.46 (2H, ddd, J = 8.1, 6.9, 1.2 Hz), 7.27 (2H, ddd, J = 8.4, 6.9, 1.3 Hz), 7.00 (2H, d, J = 8.4 Hz), 0.51 (18H, s).

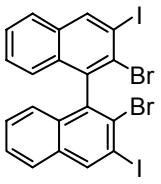
^{13}C-NMR ($CDCl_3$) δ 139.82 (C), 137.79 (C), 136.88 (CH), 133.73 (C), 131.76 (C), 129.64 (C), 128.33 (CH), 127.62 (CH), 126.13 (CH), 125.70 (CH), 0.08 (CH_3).

MS (EI, 70 eV, 110 °C): m/z (%) = 556 (100, M^+).

HRMS (EI): m/z calcd for $C_{26}H_{28}{}^{79}Br^{81}BrSi_2$: 556.0078; found: 556.0088.

3.3 2,2'-Dibromo-3,3'-diiodo-1,1'-binaphthyl (3)

3.3.1 Preparation[81]



A solution of **2** (6.45 g, 11.58 mmol) in CH_2Cl_2 (150 mL) was cooled to -40 °C and a solution of iodine monochloride (5.64 g, 34.7 mmol) in CH_2Cl_2 (60 mL) was added dropwise over 60 min. The mixture was stirred for another 45 min at –40 °C, while monitoring the reaction progress with TLC (PE).

The reaction was then quenched with 10 % $NaHSO_3$ aq. (160 mL) and allowed to warm to RT. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 80 mL). The combined organic phases were washed with water (150 mL) and brine (150 mL) and dried over $MgSO_4$. The solvents were pulled off to give **3** as yellow crystals.

Yield: 7.89 g (quantitative).

3.3.2 Analytical data

mp 243-245 °C (toluene/hexane).

^{1}H-NMR ($CDCl_3$) δ 8.59 (2H, s), 7.79 (2H, d, *J* = 8.2 Hz), 7.49 (2H, ddd, *J* = 8.2, 6.9, 1.2 Hz), 7.30 (2H, ddd, *J* = 8.4, 7.0, 1.3 Hz), 6.96 (2H, dd, *J* = 8.5, 0.7 Hz).

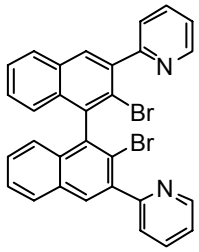
^{13}C-NMR ($CDCl_3$) δ 140.09 (CH), 139.49 (C), 133.65 (C), 131.98 (C), 128.40 (C), 128.05 (CH), 127.20 (CH), 127.15 (CH), 125.82 (CH), 98.93 (C).

MS (EI, 70 eV, 180 °C): m/z (%) = 664 (75, M^+).

HRMS (EI): m/z calcd for $C_{20}H_{10}{}^{79}Br^{81}BrI_2$: 663.7220; found: 663.7209.

3.4 2,2'-Dibromo-3,3'-bis(2-pyridyl)-1,1'-binaphthyl (7)

3.4.1 Preparation



Tetrakis(triphenylphosphine)palladium(0) (58 mg, 0.05 mmol) and **18** (250 mg, 0.5 mmol) were placed in a microwave vial under argon. A few drops of degassed ethanol were added to dissolve **18**, then 2-bromopyridine (143 µL, 1.5 mmol) and degassed DME (2 mL) were added. The suspension was briefly stirred, then Na_2CO_3 aq. (2 M, 625 µL, 1.3 mmol) was added and the biphasic system was heated to 110 °C under microwave irradiation (~64 W). After the boronic acid was consumed according to TLC analysis (PE:EtOAc, 50:50; ~6 h), the reaction mixture was partitioned between water (10 mL) and CH_2Cl_2 (10 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic phases were dried over Na_2SO_4. Removal of the solvents gave crude **7**, which was purified by flash chromatography (silica gel deactivated with $NHEt_2$, PE:EtOAc, 50:50) to yield a white solid.

Yield: 121 mg (43 %).

3.4.2 Analytical data

mp 252-254 °C (PE/EtOAc).

^{1}H-NMR ($CDCl_3$) δ 8.76 (2H, ddd, J = 4.9, 1.8, 1.0 Hz), 8.15 (2H, s), 7.95 (2H, d, J = 8.2 Hz), 7.77 (2H, ptd, J = 7.7, 1.8 Hz), 7.71 (2H, dpt, J = 7.9, 1.1 Hz), 7.50 (2H, ddd, J = 8.2, 6.9, 1.2 Hz), 7.32 (4H, m), 7.17 (2H, br d, J = 8.4 Hz).

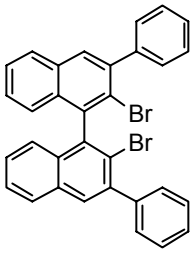
^{13}C-NMR ($CDCl_3$) δ 158.87 (C), 149.33 (CH), 139.30 (C), 139.00 (C), 135.72 (CH), 132.88 (C), 132.32 (C), 130.76 (CH), 128.51 (CH), 127.81 (CH), 126.81 (CH), 126.00 (CH), 125.45 (CH), 122.47 (CH), 122.32 (C).

MS (EI, 70 eV, 140 °C): m/z (%) = 566 (8, M^+).

HRMS (EI): m/z calcd for $C_{30}H_{18}{}^{79}Br^{81}BrN_2$: 565.9820; found: 565.9832.

3.5 2,2'-Dibromo-3,3'-diphenyl-1,1'-binaphthyl (8)

3.5.1 Preparation



Tetrakis(triphenylphosphine)palladium(0) (116 mg, 0.1 mmol) and **3** (664 mg, 1.0 mmol) were placed in a microwave vial under argon. Degassed toluene (10 mL) and phenylboronic acid (268 mg, 2.2 mmol) dissolved in a minimum amount of degassed ethanol were added. Finally Na_2CO_3 aq. (2 M, 1.25 mL, 2.5 mmol) was added and the reaction mixture heated to 110 °C for 80 min under microwave irradiation (~50 W). The reaction was monitored by TLC (PE:CH_2Cl_2, 70:30).

Upon completion of the conversion, the mixture was diluted with CH_2Cl_2 (20 mL) and water (20 mL), the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were pulled off. The crude product was purified by flash chromatography (silica gel, PE:CH_2Cl_2, 90:10) to give **8** as a white solid.

Yield: 454 mg (80 %).

3.5.2 Analytical data

mp 260-264 °C.

^{1}H-NMR ($CDCl_3$) δ 7.95 (2H, s), 7.92 (2H, d, J = 8.0 Hz), 7.57 (4H, m), 7.51 (2H, ddd, J = 8.1, 6.9, 1.2 Hz), 7.43 (6H, m), 7.32 (2H, ddd, J = 8.4, 7.0, 1.4 Hz), 7.16 (2H, d, J = 8.5 Hz).

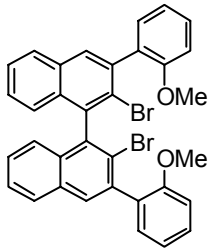
^{13}C-NMR ($CDCl_3$) δ 141.60 (C), 140.78 (C), 138.99 (C), 132.37 (2 × C), 129.97 (CH), 129.90 (CH), 128.20 (CH), 127.88 (CH), 127.63 (CH), 127.32 (CH), 126.71 (CH), 125.92 (CH), 123.84 (C).

MS (EI, 70 eV, 170 °C): m/z (%) = 564 (15, M^+).

HRMS (EI): m/z calcd for $C_{32}H_{20}{}^{79}Br^{81}Br$: 563.9915; found: 563.9923.

3.6 2,2'-Dibromo-3,3'-bis(2-methoxyphenyl)-1,1'-binaphthyl (9)

3.6.1 Preparation



Method a) Thermic reaction conditions

Toluene (2 mL) was added to **3** (133 mg, 200 µmol) and the solution was degassed. Tetrakis(triphenylphosphine)palladium(0) (11.6 mg, 10 µmol) and 2-methoxyphenylboronic acid (64 mg, 500 µmol) dissolved in a minimum amount of degassed ethanol were added. Finally Na_2CO_3 aq. (2 M, 250 µL, 500 µmol) was added and the mixture was refluxed for 4 days. The reaction was monitored *via* TLC (PE:CH_2Cl_2, 70:30).

Upon completion of the conversion, the solvents were pulled off and the residue was redissolved in CH_2Cl_2 (5 mL). Water (5 mL) was added, the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were filtered through a silica plug (CH_2Cl_2), dried over $MgSO_4$ and the solvents were pulled off. The crude product was purified by flash chromatography (silica gel, PE:CH_2Cl_2, gradient 70:30 → 50:50) to give **9**, a white crystalline solid which was pure by TLC and HPLC analysis.

Yield: 94 mg (75 %).

Method b) Microwave conditions

Tetrakis(triphenylphosphine)palladium(0) (58 mg, 0.05 mmol), **3** (332 mg, 0.5 mmol) and 2-methoxyphenylboronic acid (228 mg, 1.5 mmol) were placed in a microwave vial under argon. Degassed ethanol (0.5 mL), degassed DME (2.5 mL) and then Na_2CO_3 aq. (2 M, 0.65 mL, 1.3 mmol) were added. The solution was heated to 110 °C for 12 h under microwave irradiation (~45 W). Thereafter, TLC analysis showed complete conversion. Workup proceeded as in *Method a)* above.

Yield: 127 mg (41 %).

3.6.2 Analytical data

mp 125-128 °C (PE/CH_2Cl_2).

The following NMR spectra were recorded at 360 K in DMSO-d_6.

^{1}H-NMR (DSMO-d_6) δ 9.14 (2H, d, *J* = 8.2 Hz), 9.09 (2H, s), 8.66 (2H, pt, *J* = 7.5 Hz), 8.55-8.48 (4H, m), 8.45 (2H, dd, *J* = 7.4, 1.5 Hz), 8.23 (2H, d, *J* = 8.3 Hz), 8.19 (4H, pt, *J* = 7.4 Hz), 4.85 (6H, s).

^{13}C-NMR (DMSO-d_6) δ 156.53 (C), 137.41 (C), 137.13 (C), 131.80 (C), 131.43 (C), 130.20 (C), 130.02 (CH), 129.49 (CH), 129.10 (CH), 127.82 (CH), 126.77 (CH), 126.02 (CH), 124.75 (C), 124.67 (CH), 119.95 (CH), 111.51 (CH), 55.37 (CH_3).

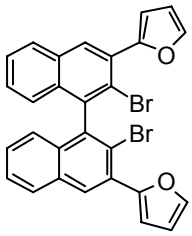
MS (EI, 70 eV, 120 °C): m/z (%) = 624 (100, M^+).

HRMS (EI): m/z calcd for $C_{34}H_{24}{}^{79}Br^{81}BrO_2$: 624.0120; found: 624.0126.

Further NMR experiments (at different temperatures) confirmed that **9** is a mixture of rotamers, interconverting at RT; cf. p. 22.

3.7 2,2'-Dibromo-3,3'-bis(2-furyl)-1,1'-binaphthyl (11)

3.7.1 Preparation[73]



Tetrakis(triphenylphosphine)palladium(0) (116 mg, 0.1 mmol), **3** (664 mg, 1 mmol) and 2-furylboronic acid (336 mg, 3 mmol) were placed in a microwave vial under argon. Degassed ethanol (0.5 mL), degassed DME (4 mL) and then Na_2CO_3 aq. (2 M, 1.25 mL, 2.5 mmol) were added. The mixture was heated to 120 °C for 1 h under microwave irradiation (~36 W), then for further 7.5 h to 110 °C (~34 W). Thereafter, TLC analysis still showed remaining starting material, but black precipitate indicated decomposition of the catalyst. Thus, the mixture was diluted with CH_2Cl_2 (10 mL) and water (10 mL), the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic phases were washed with water (20 mL) and dried over $MgSO_4$. Removal of the solvents gave the crude product, which was filtered through a silica plug (CH_2Cl_2) and purified by flash chromatography (silica gel, PE:CH_2Cl_2, 90:10) to give **11** as a yellow powder.

Yield: 65 mg (12 %).

3.7.2 Analytical data

mp 193-195 °C.

^{1}H-NMR ($CDCl_3$) δ 8.40 (2H, s), 7.96 (2H, d, J = 8.2 Hz), 7.60 (2H, dd, J = 1.8, 0.5 Hz), 7.50 (2H, ddd, J = 8.1, 6.9, 1.1 Hz), 7.28 (2H, ddd, J = 8.4, 7.0, 1.3 Hz), 7.21 (2H, d, J = 3.4 Hz), 7.06 (2H, dd, J = 8.4, 0.6 Hz), 6.56 (2H, dd, J = 3.4, 1.8 Hz).

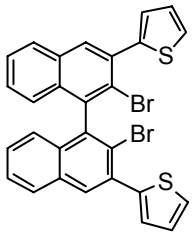
^{13}C-NMR ($CDCl_3$) δ 151.86 (C), 142.43 (CH), 139.69 (C), 132.31 (C), 132.17 (C), 129.37 (C), 128.63 (CH), 128.52 (CH), 127.64 (CH), 126.90 (CH), 125.81 (CH), 120.80 (C), 111.49 (CH), 111.27 (CH).

MS (EI, 70 eV, 110 °C): m/z (%) = 544 (100, M^+).

HRMS (EI): m/z calcd for $C_{28}H_{16}O_2{}^{81}Br_2$: 545.9506; found: 545.9486.

3.8 2,2'-Dibromo-3,3'-bis(2-thienyl)-1,1'-binaphthyl (12)

3.8.1 Preparation[73]



Tetrakis(triphenylphosphine)palladium(0) (116 mg, 0.1 mmol), **3** (664 mg, 1 mmol) and 2-thienylboronic acid (384 mg, 3 mmol) were placed in a microwave vial under argon. Ethanol (0.5 mL), DME (4 mL) and then Na_2CO_3 aq. (2 M, 1.25 mL, 2.5 mmol) were added. The mixture was heated to 120 °C for 2.5 h under microwave irradiation (~20 W). Thereafter, TLC analysis still showed remaining starting material, but black precipitate indicated decomposition of the catalyst. Thus, the mixture was diluted with CH_2Cl_2 (10 mL) and water (10 mL), the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with water (20 mL) and dried over $MgSO_4$. Removal of the solvents gave the crude product, which was filtered through a silica plug (CH_2Cl_2) and purified by flash chromatography (silica gel, PE:CH_2Cl_2, 70:30) to give **12** as a white solid.

Yield: 352 mg (61 %).

3.8.2 Analytical data

mp 212-215 °C.

^{1}H-NMR ($CDCl_3$) δ 8.13 (2H, s), 7.92 (2H, d, J = 8.2 Hz), 7.51 (2H, ddd, J = 8.1, 6.9, 1.1 Hz), 7.42 (4H, m), 7.33 (2H, ddd, J = 8.4, 7.0, 1.3 Hz), 7.14 (2H, dd, J = 5.1, 3.6 Hz), 7.13 (2H, d, J = 8.9 Hz).

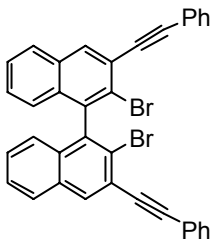
^{13}C-NMR ($CDCl_3$) δ 142.14 (C), 139.34 (C), 133.32 (C), 132.43 (C), 132.20 (C), 131.21 (CH), 128.48 (CH), 128.27 (CH), 127.74 (CH), 126.92 (2 × CH), 126.15 (CH), 125.86 (CH), 123.80 (C).

MS (EI, 70 eV, 120 °C): m/z (%) = 576 (20, M^+).

HRMS (EI): m/z calcd for $C_{28}H_{16}S_2{}^{79}Br^{81}Br$: 575.9042; found: 575.9030.

3.9 2,2'-Dibromo-3,3'-bis(phenylethynyl)-1,1'-binaphthyl (14)

3.9.1 Preparation[63]



Ethynylbenzene (1.65 mL, 1.53 g, 15 mmol) was dissolved in dry THF (50 mL) in a Schlenk flask and the solution was degassed. After cooling to 0 °C under argon, *n*-butyllithium (11.25 mL, 18 mmol) was added, upon which the color changed to dark green. The mixture was stirred at 0 °C for 30 min, then zinc chloride (18.00 mL, 18 mmol) was added to give a yellow-brown solution, followed by further 30 min of stirring at 0 °C. Tetrakis(triphenylphosphine)palladium(0) (58 mg, 0.05 mmol) and **3** (664 mg, 1 mmol) were added and the solution was heated to 65 °C. The color of the mixture rapidly changed to yellow. Reaction progress was monitored by TLC (PE:CH_2Cl_2, 90:10) and after complete consumption of the starting material (usually less then 1 h) the mixture was quenched with HCl aq. (4 M, 80 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were pulled off. The crude product was filtered over a silica plug (PE:CH_2Cl_2, 70:30). Subsequently the product was purified by flash chromatography (silica gel, PE:CH_2Cl_2, 90:10) to yield an orange crystalline solid.

Yield: 521 mg (85 %).

3.9.2 Analytical data

mp 171-174 °C.

^{1}H-NMR ($CDCl_3$) δ 8.27 (2H, s), 7.90 (2H, d, J = 8.1 Hz), 7.62 (4H, m), 7.51 (2H, ddd, J = 8.1, 7.0, 1.0 Hz), 7.36 (6H, m), 7.31 (2H, ddd, J = 8.3, 7.0, 1.2 Hz), 7.05 (2H, d, J = 8.4 Hz).

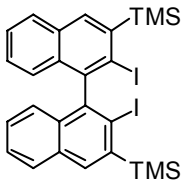
^{13}C-NMR ($CDCl_3$) δ 138.21 (C), 133.30 (CH), 132.39 (C), 132.12 (C), 131.73 (CH), 128.68 (CH), 128.41 (CH), 128.15 (CH), 128.08 (CH), 127.01 (CH), 125.84 (CH), 124.63 (C), 123.31 (C), 122.97 (C), 93.91 (C), 88.67 (C).

MS (ESI, MeOH/MeCN): m/z (%) = 633 (36, $[M+Na]^+$).

HRMS (EI): m/z calcd for $C_{36}H_{20}{}^{79}Br^{81}Br$: 611.9916; found: 611.9905.

3.10 2,2'-Diiodo-3,3'-bis(trimethylsilyl)-1,1'-binaphthyl (15)

3.10.1 Preparation



Dry THF (20 mL) was added to **2** (0.90 g, 1.6 mmol) and the solution was degassed. After cooling to –78 °C under argon, *n*-butyllithium (1.6 M in hexanes, 3.0 mL, 4.9 mmol) was added and the mixture was stirred for 1 h. After addition of iodine (1.64 g, 6.5 mmol) stirring was continued for another 1 h at –78 °C. The reaction was quenched with 10 % $NaHSO_3$ aq. (20 mL) and warmed to RT. After dilution with EtOAc (20 mL) and water (20 mL) the phases were separated and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic phases were washed with water (50 mL) and dried over $MgSO_4$. The solvents were pulled off to give **15** as a slightly yellow foam. Since it was found to be pure by NMR and TLC, no further purification was performed.

Yield: 1.07 g (quantitative)

3.10.2 Analytical data

mp 93-95 °C

^{1}H-NMR ($CDCl_3$) δ 8.01 (2H, s), 7.89 (2H, d, J = 8.2 Hz), 7.47 (2H, ddd, J = 8.1, 6.9, 1.2 Hz), 7.25 (2H, ddd, J = 8.4, 6.9, 1.4 Hz), 7.00 (2H, d, J = 8.4 Hz), 0.55 (18H, s).

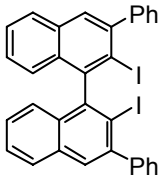
^{13}C-NMR ($CDCl_3$) δ 146.01 (C), 143.90 (C), 136.80 (CH), 133.15 (C), 132.24 (C), 128.29 (CH), 127.64 (CH), 126.43 ($2 \times$ CH), 108.66 (C), 0.43 (CH_3).

MS (EI, 70 eV, 120 °C): m/z (%) = 650 (74, M^+).

HRMS (EI): m/z calcd for $C_{26}H_{28}I_2Si_2$: 649.9819; found: 649.9798.

3.11 2,2'-Diiodo-3,3'-diphenyl-1,1'-binaphthyl (16)

3.11.1 Preparation



Dry THF (10 mL) was added to **8** (338 mg, 0.6 mmol) and the solution was degassed. After cooling to –78 °C under argon, *n*-butyllithium (1.6 M in hexanes, 1.9 mL, 3 mmol) was added and the mixture was stirred for 1 h. After addition of 1,2-diiodoethane (845 mg, 3 mmol) in dry THF (5 mL), stirring was continued and the solution was allowed to warm to RT overnight.

The reaction was quenched with 10 % $NaHSO_3$ aq. (20 mL). After dilution with EtOAc (20 mL) and water (20 mL) the phases were separated and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic phases were washed with water (50 mL) and dried over $MgSO_4$. The solvents were pulled off to give the crude product. After column chromatography (silica gel, PE:CH_2Cl_2, 90:10) **16** was obtained as a slightly yellow solid.

Yield: 344 mg (87 %)

3.11.2 Analytical data

mp 209-211 °C.

^{1}H-NMR ($CDCl_3$) δ 7.91 (2H, s), 7.90 (2H, d, J = 8.2 Hz), 7.74-7.39 (12H, m), 7.31 (2H, ddd, J = 8.4, 7.0, 1.3 Hz) 7.17 (2H, d, J = 8.5 Hz).

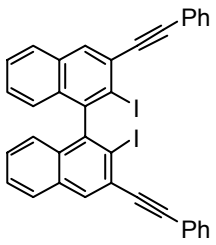
^{13}C-NMR ($CDCl_3$) δ 146.95 (C), 144.98 (C), 144.40 (C), 133.02 (C), 131.87 (C), 129.87 (CH), 128.28 (CH), 128.12 (CH), 127.82 (CH), 127.66 (CH), 127.27 (CH), 126.98 (CH), 126.60 (CH), 105.69 (C).

MS (EI, 70 eV, 180 °C): m/z (%) = 658 (97, M^+).

HRMS (EI): m/z calcd for $C_{32}H_{20}I_2$: 657.9654; found: 657.9671.

3.12 2,2'-Diiodo-3,3'-bis(phenylethynyl)-1,1'-binaphthyl (17)

3.12.1 Preparation



Dry THF (10 mL) was added to **14** (457 mg, 0.74 mmol) and the solution was degassed. After cooling to –78 °C under argon, *n*-butyllithium (1.6 M in hexane, 1.67 mL, 2.67 mmol) was added to give a dark red mixture. After 1 h of stirring, iodine (906 mg, 3.57 mmol) was added and the solution was stirred for another 1 h.
The reaction was then quenched with $NaHSO_3$ aq. sat. (25 mL). After warming to RT, the mixture was partitioned between EtOAc (50 mL) and water (25 mL). The phases were separated and the organic layer was washed with water. If the combined aqueous phases were found to still contain product (TLC), they were extracted with EtOAc (2 × 25 mL) again. The combined organic phases were dried over $MgSO_4$ and the solvents were pulled off. The crude product was purified by flash chromatography (silica gel, PE:CH_2Cl_2, 90:10) to give **17** as a white solid.
Yield: 171 mg (33 %)

3.12.2 Analytical data

mp 190-193 °C

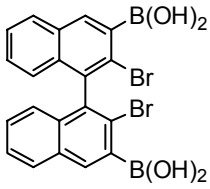
^{1}H-NMR ($CDCl_3$) δ 8.24 (2H, s), 7.90 (2H, d, J = 8.2 Hz), 7.64 (4H, m), 7.51 (2H, ddd, J = 8.2, 6.9, 1.1 Hz), 7.36 (6H, m), 7.28 (2H, ddd, J = 8.4, 7.0, 1.2 Hz), 7.05 (2H, d, J = 8.4 Hz).

^{13}C-NMR ($CDCl_3$) δ 146.31 (C), 132.86 (C), 132.14 (CH), 131.89 (C), 131.62 (CH), 128.67 (CH), 128.41 (CH), 128.09 (CH), 128.03 (CH), 127.24 (CH), 127.21 (C), 126.44 (CH), 123.02 (C), 105.48 (C), 93.14 (C), 92.50 (C).

MS (EI, 70 eV, 170 °C): m/z (%) = 705 (3, M^+), 579 (13, $[M\text{-}I]^+$).

3.13 2,2'-Dibromo-1,1'-binaphthyl-3,3'-diyldiboronic acid (18)

3.13.1 Preparation



2,2,6,6-Tetramethylpiperidine (1.02 mL, 874 mg, 6 mmol) in dry THF (10 mL) was degassed and *n*-butyllithium (3.75 mL, 6 mmol) was added dropwise at 0 °C under argon. After 20 min the solution was cooled to –78 °C and triisopropyl borate (2.31 mL, 1.88 g, 10 mmol) was added through a septum. After another 10 min, **1** (412 mg, 1 mmol) in degassed THF (7 mL) was added dropwise *via* a Teflon cannula. The solution was stirred for several hours while slowly warming to about –45 °C. It was cooled to –78 °C and triisopropyl borate (1.15 mL, 940 mg, 5 mmol) was added. The solution was then allowed to warm to RT over 6-8 h.

The reaction was quenched with HCl aq. (1 M, 30 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic phases were then extracted with NaOH aq. (1M, 3 × 60 mL). The combined basic extracts were acidified with 2 M HCl aq. and extracted with EtOAc (3 × 60 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated to provide **18** as an off-white to brown crystalline solid.

Yield: 448 mg (90 %).

3.13.2 Analytical data

mp 159-161 °C.

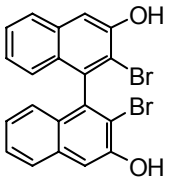
^{1}H-NMR (methanol-d_4) δ 7.99 (2H, d, J = 8.2 Hz), 7.96 (2H, s), 7.52 (2H, ddd, J = 8.1, 7.0, 1.0 Hz), 7.31 (2H, ddd, J = 8.4, 7.0, 1.1 Hz), 6.99 (2H, d, J = 8.5 Hz).

^{13}C-NMR (DMSO-d_6) δ 128.42 (C), 125.18 (C), 124.59 (CH), 124.13 (C), 119.98 (CH), 119.16 (CH), 118.10 (CH), 117.05 (CH), 116.53 (C).[ii]

[ii] One quaternary carbon was not observed.

3.14 2,2'-Dibromo-,3,3'-dihydroxy-1,1'-binaphthyl (19)

3.14.1 Preparation



Diboronic acid **18** (201 mg, 0.4 mmol) was stirred with H_2O_2 (30 %, 0.1 mL, 1 mmol) in water (0.7 mL) / methanol (2.5 mL) at RT overnight. Extractive workup with EtOAc (20 mL) and water (20 mL) left a crude product which was purified by column chromatography (silica gel, PE:EtOAc, 70:30) to give **19** as a slightly yellow solid.
Yield: 129 mg (76 %).

3.14.2 Analytical data

mp 243-247 °C.

^{1}H-NMR (DMSO-d_6) δ 10.73 (2H, bs), 7.83 (2H, d, J = 8.2 Hz), 7.47 (2H, s), 7.42 (2H, pt, J = 7.5 Hz), 7.10 (2H, pt, J = 7.6 Hz), 6.76 (2H, d, J = 8.4 Hz).

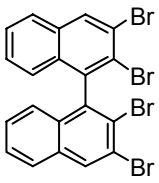
^{13}C-NMR (DMSO-d_6) δ 151.72 (C), 138.65 (C), 133.52 (C), 126.90 (C), 126.59 (CH), 126.47 (CH), 125.02 (CH), 124.08 (CH), 115.77 (C), 109.86 (CH).

MS (EI, 70 eV, 120 °C): m/z (%) = 444 (94, M^+).

HRMS (EI): m/z calcd for $C_{20}H_{12}{}^{79}Br_2O_2$: 441.9204; found: 441.9197.

3.15 2,2',3,3'-Tetrabromo-1,1'-binaphthyl (20)

3.15.1 Preparation[74]



N-Bromosuccinimide (445 mg, 2.5 mmol) was added to **2** (556 mg, 1 mmol) in acetonitrile (5 mL) and the resulting yellow suspension was stirred at RT. Reaction progress was monitored by TLC (PE). Waiting for complete consumption of the starting material was found to be essential, as later separation is difficult due to the poor solubility of the product. Upon completion of the conversion, the solvent was pulled off and the residue was partitioned between toluene (~ 150 mL) and HCl aq. (1 M, ~ 75 mL). The phases were separated and the solvents of the organic phase were pulled off.

If the starting material was consumed completely in the reaction, the crude product was usually very pure and was used without further purification. Otherwise purification by flash chromatography (silica gel, PE; the crude mixture was dry loaded due to poor solubility in the eluent) yielded **20** as a slightly yellow powder.

Yield: 581 mg (quantitative).

3.15.2 Analytical data

mp 214-218 °C.[iii]

^{1}H-NMR ($CDCl_3$) δ 8.33 (2H, s), 7.83 (2H, d, J = 8.3 Hz), 7.51 (2H, ddd, J = 8.2, 6.9, 1.1 Hz), 7.30 (2H, ddd, J = 8.4, 7.0, 1.3 Hz), 6.97 (2H, d, J = 8.5 Hz).

^{13}C-NMR ($CDCl_3$) δ 140.02 (C), 133.23 (C), 132.71 (CH), 131.52 (C), 127.86 (CH), 127.42 (CH), 127.39 (CH), 125.82 (CH), 124.67 (C), 122.63 (C).

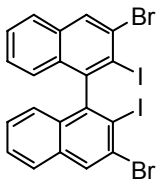
MS (EI, 70 eV, 130 °C): m/z (%) = 570 (49, M^+).

HRMS (EI): m/z calcd for $C_{20}H_{10}{}^{79}Br_4$: 565.7516; found: 565.7519.

[iii] Some crystals melted at 102-106 °C.

3.16 2,2'-Diiodo-3,3'-dibromo-1,1'-binaphthyl (21)

3.16.1 Preparation[74]



N-Bromosuccinimide (616 mg, 3.5 mmol) was added to **15** (900 mg, 1.4 mmol) in acetonitrile (7 mL) and the resulting orange suspension was stirred at RT. Reaction progress was monitored by TLC (PE). Waiting for complete consumption of the starting material was found to be essential, as later separation is difficult due to the poor solubility of the product.

Upon completion of the conversion, the solvent was pulled off and the residue was partitioned between toluene (~ 150 mL) and HCl aq. (1 M, ~ 75 mL). The phases were separated and the solvents of the organic phase were pulled off.

The crude product was purified by flash chromatography (silica gel, PE; the crude mixture was dry loaded due to poor solubility in the eluent) to yield **21** as a white solid.

Yield: 778 mg (85 %).

3.16.2 Analytical data

mp 250-253 °C.

^{1}H-NMR ($CDCl_3$) δ 8.33 (2H, s), 7.83 (2H, d, J = 8.3 Hz), 7.51 (2H, ddd, J = 8.2, 6.9, 1.1 Hz), 7.28 (2H, ddd, J = 8.4, 7.0, 1.3 Hz), 6.96 (2H, d, J = 8.5 Hz).

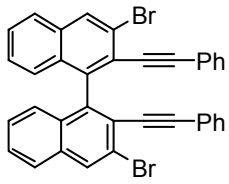
^{13}C-NMR ($CDCl_3$) δ 148.67 (C), 134.11 (C), 131.34 (CH), 130.81 (C), 127.80 (CH), 127.62 (CH), 127.35 (CH), 127.07 (C), 126.49 (CH), 106.70 (C).

MS (EI, 70 eV, 210 °C): m/z (%) = 664 (60, M^+).

HRMS (EI): m/z calcd for $C_{20}H_{10}{}^{79}Br_2I_2$: 661.7239; found: 661.7225.

3.17 3,3'-Dibromo-2,2'-bis(phenylethinyl)-1,1'-binaphthyl (22)

3.17.1 Preparation



Ethynylbenzene (0.8 mL, 766 mg, 7.5 mmol) was dissolved in dry THF (25 mL) in a Schlenk flask and the solution was degassed. After cooling to 0 °C under argon, *n*-butyllithium (2.5 M in hexanes, 3.6 mL, 9 mmol) was added, upon which the color changed to dark green. The mixture was stirred at 0 °C for 30 min, then zinc chloride (1 M in Et_2O, 9.00 mL, 9 mmol) was added to give a yellow-brown solution and stirring was continued for further 30 min at 0 °C.

Tetrakis(triphenylphosphine)palladium(0) (29 mg, 0.025 mmol) and **21** (332 mg, 0.5 mmol) were added, the solution was slowly warmed to RT, whereupon the color of the mixture changed to black.

Reaction progress was monitored by TLC (PE:CH_2Cl_2, 90:10) and after complete consumption of the starting material (12 h) the mixture was quenched with HCl aq. (4 M, 25 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were pulled off. The crude product was purified by flash chromatography (silica gel, PE:CH_2Cl_2, 90:10) to give **22** as an orange crystalline solid.

Yield: 22 mg (7 %).

3.17.2 Analytical data

mp 215-220 °C.

^{1}H-NMR ($CDCl_3$) δ 8.29 (2H, s), 7.85 (2H, d, *J* = 8.2 Hz), 7.49 (2H, ddd, *J* = 8.1, 6.8, 1.3 Hz), 7.33 (2H, ddd, *J* = 8.3, 6.9, 1.3 Hz), 7.26 (2H, d, *J* = 8.4 Hz), 7.16-7.09 (6H, m), 6.83 (4H, dm, *J* = 5.6 Hz).

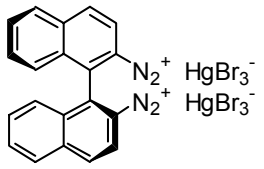
^{13}C-NMR ($CDCl_3$) δ 141.53 (C), 133.54 (C), 131.34 (CH), 131.19 (C), 131.12 (CH), 128.31 (CH), 128.01 (CH), 127.53 (CH), 127.24 (CH), 127.17 (CH), 126.55 (CH), 123.62 (C), 122.74 (C), 121.70 (C), 98.13 (C), 87.65 (C).

MS (EI, 70 eV, 170 °C): m/z (%) = 612 (29, M^+).

HRMS (EI): m/z calcd for $C_{36}H_{20}{}^{79}Br^{81}Br$: 611.9916; found: 611.9912.

3.18 1,1'-Binaphthyl-2,2'-bis(diazonium) tribromomercurate (24)[75]

3.18.1 Preparation



Sodium nitrite (5.74 g, 83.0 mmol) was slowly added to sulfuric acid (190 mL) at –5 °C, avoiding NO_2 gas evolution. Upon complete addition, the solution was warmed to RT until dissolution of the salt completed. After cooling back to –10 °C, (*S*)-**23** (5.00 g, 17.6 mmol) in pyridine (35 mL) was added dropwise over 2-3 h, keeping the temperature below –5 °C. Stirring was continued for 1 h below –5 °C, then ice chunks were added slowly to dilute the acid while keeping the temperature low. When no more temperature rise was observed during ice addition, urea (5.02 g, 84.0 mmol) in water (125 mL) was slowly added below –5 °C, whereupon a thick yellow foam formed. After 30 min stirring, $HgBr_2$ (17.81 g, 49.4 mmol) and KBr (17.79 g, 149 mmol) dissolved in water (100 mL) was added. The solution was stirred another 30 min at –5 °C, then the yellow precipitate was filtered and washed with water until the fresh filtrates were not acidic any more. The solids were further washed with a minimum of methanol followed by ether, then dried by suction to yield **24** as yellow powder.

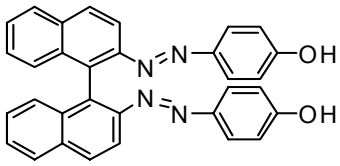
Yield: 20.89 g (quantitative)

3.18.2 Analytical data

Analytical properties of this reactive intermediate were not determined. Optical appearance and reactivity matched the literature data.[75]

3.19 2,2'-Bis(2-(4-hydroxyphenyl)diazenyl)-1,1'-binaphthyl (26)

3.19.1 Preparation



Phenol (792 mg, 8.41 mmol) and **24** (1.00 g, 0.84 mmol) were dissolved in methanol (12 mL). NaOH (34 mg, 0.84 mmol) was added and the solution was stirred at RT in the dark while monitoring reaction progress *via* TLC (PE:EtOAc, 50:50).

After about 90 min NH_4Cl aq. sat. (~50 mL) and CH_2Cl_2 (~50 mL) were added. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2×30 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were pulled off. The crude product was purified by flash chromatography (silica gel, PE:EtOAc, 70:30) to yield the product as an orange solid.

Yield: 215 mg (52 %).

3.19.2 Analytical data

mp 129-130 °C.

^{1}H-NMR (methanol-d_4) δ 8.08 (2H, d, J = 9.0 Hz), 8.05 (2H, d, J = 9.0 Hz), 7.98 (2H, d, J = 8.1 Hz), 7.47 (2H, ddd, J = 8.1, 6.8, 1.2 Hz), 7.35 (2H, d, J = 8.3 Hz), 7.25 (2H, ddd, J = 8.3, 6.9, 1.3 Hz), 7.19 (4H, d, J = 8.9 Hz), 6.61 (4H, d, J = 8.9 Hz).

^{13}C-NMR (methanol-d_4) δ 161.55 (C), 149.62 (C), 147.86 (C), 137.48 (C), 135.56 (C), 135.49 (C), 130.03 (CH), 129.18 (CH), 128.45 (CH), 127.98 (CH), 127.61 (CH), 125.67 (CH), 116.34 (CH), 115.37 (CH).

MS (EI, 70 eV, 180 °C): m/z (%) = 494 (4, M^+).

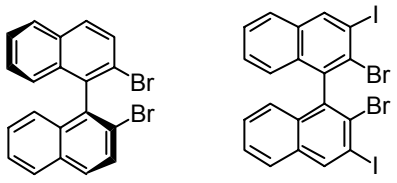
Crystals for X-ray structure determination were obtained by recrystallization from PE:CH_2Cl_2.

4 Conclusion

Ortho-metallation of racemic 2,2'-dibromo-1,1'-binaphthyl (**1**) was shown to be a viable way of introducing boronic acid functionality or trimethylsilyl (TMS) groups in 3,3' position. Both of these groups allowed further functionalization: the boronic acid could be oxidized to the corresponding dihydroxy compound or could be used to introduce aromatic moieties *via* Suzuki coupling. The TMS group on the other hand, was a convenient handle for *ipso*-substitution and allowed even more flexible functionalization: for example, introduction of bromo or iodo substituents, furnishing various tetrahalo-1,1'-binaphthyls in high yield. Especially, **3** was an interesting compound, as it could be regioselectively derivatized in 3,3' position using transition metal catalyzed cross coupling reactions, such as Suzuki and Negishi couplings. Subsequent substitution in 2,2' position was shown to be possible by lithium halogen exchange.

After problems reproducing procedures for the stereoconservative synthesis of **1** starting from enantiopure 2,2'-diamino-1,1'-binaphthyl (DABN), a novel approach was sought. As the synthesis of the diazonium intermediate used in literature methods worked well, investigations focused on the subsequent decomposition step yielding **1**. Following the initial idea of utilizing UV irradiation, a wide variety of reaction conditions were screened. During those efforts, a method to analyze the enantiomeric purity of the diazonium intermediate was devised: azo coupling with phenol gave a product whose enantiomers were readily separable *via* chiral HPLC. The optimum conditions found for the synthesis of **1** turned out to be reproducible and high yielding, and this method continually furnished material with high enantiomeric excess (~94 %).

To conclude, 13 new binaphthyl derivatives were synthesized and characterized, and an innovative, high yielding route to enantiopure **1** was developed.



(*S*)-**1** **3**

Figure 22. The two main topics of this thesis: enantiopure **1** and binaphthyl analoga with **3** as central intermediate.

Future work could focus on the influence of 3,3’ substituents on racemization behavior during lithium halogen exchange reactions in 2,2’ position. Especially complexing groups could alter the geometry of the dilithium intermediate (cf. p. 14), which might prevent loss of enantiomeric purity. These investigations seem straightforward, now that an enantioconservative route to advanced intermediates starting from readily available DABN has been worked out.

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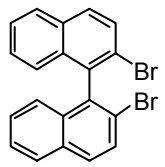
6 Appendix

6.1 Structure index



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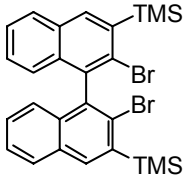

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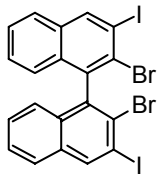

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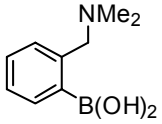

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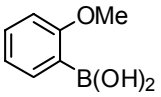

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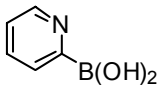

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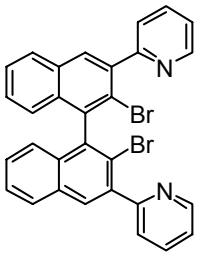

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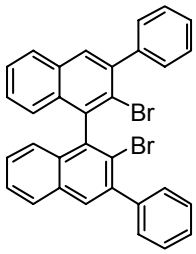

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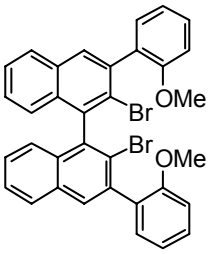

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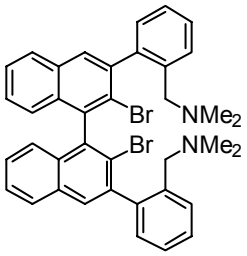

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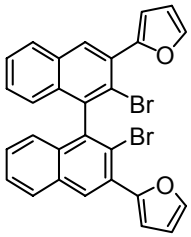

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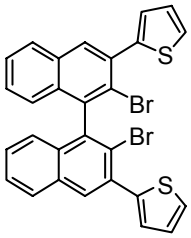

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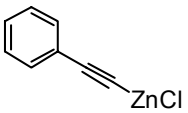

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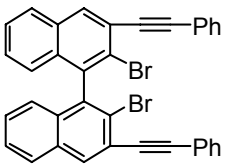

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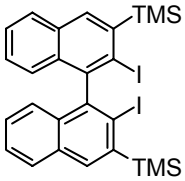

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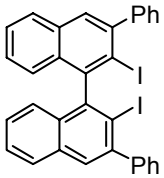

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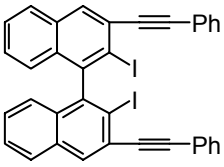

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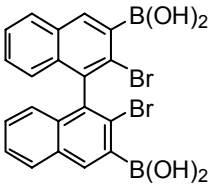

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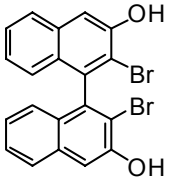

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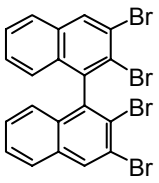

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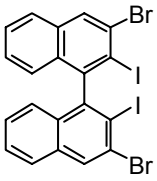

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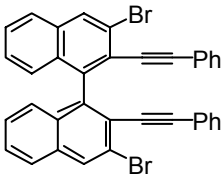

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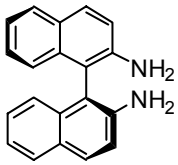

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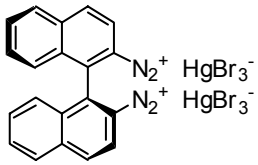

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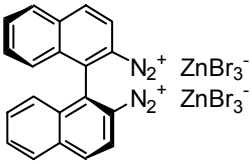

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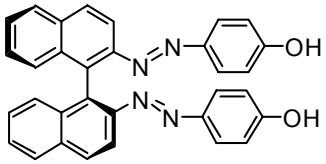

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6.2 Abstract (german)

In racemisches 2,2'-Dibrom-1,1'-binaphthyl (DBBN) wurden durch *ortho*-Metallierung Trimethylsilyl- (TMS) und Borsäuregruppen in 3,3' Position eingeführt. Die Borsäure konnte entweder zu der entsprechenden 3,3'-Dihydroxy Verbindung oxidiert, oder unter Suzuki Bedingungen gegen aromatische Reste ausgetauscht werden. Die 3,3'-TMS Verbindung erlaubte durch *ipso*-Substitution die Synthese mehrerer Tetrahalo-1,1'-binaphthyle in hohen Ausbeuten. Von diesen erwies sich besonders 2,2'-Dibrom-3,3'-diiod-1,1'-binaphthyl als flexible Zwischenstufe, welche durch übergangsmetallkatalysierte Kreuzkupplungen regioselektiv in 3,3' Position derivatisiert werden konnte. Durch Lithium-Halogen Austausch in 2,2' Position konnten aus diesen Produkten wiederum mehrere neue Verbindungen hergestellt werden.

Im Rahmen dieser Versuche kam der Bedarf für enantiomerenreines DBBN auf. Nachdem zwei Vorschriften für dessen Synthese ausgehend von nicht-racemischem 2,2'-Diamino-1,1'-binaphthyl (DABN) nur Produkt von schlechter enantiomerer Reinheit lieferten, wurden alternative Wege untersucht. Da die Darstellung der Diazonium-Zwischenstufe (die in den literaturbekannten Methoden verwendet wurde) in guten Ausbeuten gelang, schien die Suche nach einem neuen Ansatz für dessen Zersetzung zu DBBN vielversprechend. Nachdem photochemischer Abbau durch UV Licht in ersten Versuchen gelang, wurden zahlreiche Reaktionsbedingungen untersucht um Ausbeute und Enantiomerenreinheit zu optimieren. Um den Enantiomerenüberschuss des Diazoniumsaltzes zu bestimmen, wurde dieses mit Phenol in die entsprechenden Azoverbindung umgewandelt, welche mittels chiraler HPLC getrennt werden konnte. Die so entwickelte Methode war gut reproduzierbar und gab DBBN in guten Ausbeuten und Enantiomerenüberschüssen (~94 %).

Zusammenfassend wurden im Rahmen dieser Arbeit 13 neue Binaphthyl Derivate hergestellt und charakterisiert und es wurde eine innovative Syntheseroute zu enantiomerenreinem DBBN entwickelt.

6.3 Curriculum vitae (german)

Persönliche Daten:

Christian Aichinger

Hauptstraße 44a, 3373 Kemmelbach

geb. am 20. Juli 1984 in St. Pölten

Schulbildung:

1990 – 1994	Volksschule in Ybbs/Donau
1994 – 2002	BG/BRG Wieselburg
Juni 2002	Matura mit gutem Erfolg bestanden

Studium:

Seit WS 2002	Studium der Chemie
WS 2004 – SS 2005	Beurlaubt vom Studium zur Ableistung des Zivildienstes
WS 2006	Abschluss des 1. Studienabschnitts
SS 2007	Auslandssemester an der „Lunds Universitet“ in Lund/Schweden
SS 2008	Diplomarbeit unter Prof. Dr. M. Widhalm